

FINAL REPORT

Test Facility Study No. 514867

Repeated Dose 28-Day Oral Toxicity Study with MLA-3202 by Daily Gavage in the Rat

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03 March 2017

Page 1 of 176

TABLE OF CONTENTS

LIST OF APPENDICES	3
1. STATEMENT OF GLP COMPLIANCE.....	4
2. TEST FACILITY QUALITY ASSURANCE STATEMENT	5
3. SUMMARY	7
4. INTRODUCTION	9
4.1. Study Schedule.....	9
4.2. Purpose.....	9
4.3. Guidelines	9
4.4. Retention of Records and Materials.....	10
4.5. Responsible Personnel	10
4.5.1. Test Facility	10
4.5.2. Sponsor Representative.....	10
4.5.3. Data Collection	10
5. MATERIALS AND METHODS	11
5.1. Test Item	11
5.1.1. Test Item Information	11
5.1.2. Study Specific Item Information.....	11
5.2. Vehicle Information	11
5.3. Test Item Preparation.....	11
5.4. Chemical Analysis of Dose Preparations.....	12
5.5. Test System.....	12
5.6. Allocation.....	12
5.7. Animal Husbandry	13
5.8. Treatment	13
5.9. Observations	14
5.10. Clinical Laboratory Investigations.....	15
5.11. Pathology	16
5.11.1. Necropsy	16
5.11.2. Organ Weights	17
5.11.3. Histotechnology	17
5.11.4. Histopathology	17
5.12. Interpretation.....	17
5.13. List of Deviations.....	18
5.13.1. List of Study Plan Deviations	18
5.13.2. List of Standard Operating Procedures Deviations.....	18
6. ELECTRONIC SYSTEMS FOR DATA ACQUISITION.....	19
7. RESULTS	20
7.1. Analysis of Dose Preparations	20
7.2. Observations	20
7.2.1. Mortality	20
7.2.2. Clinical Signs	20
7.2.3. Functional Observations	20
7.2.4. Body Weight	20
7.2.5. Food Consumption.....	21
7.3. Clinical Laboratory Investigations.....	21
7.3.1. Haematology	21

7.3.2.	Clinical Biochemistry	21
7.4.	Pathology	21
7.4.1.	Macroscopic Examination	21
7.4.2.	Organ Weights	21
7.4.3.	Microscopic Examination	22
8.	DISCUSSION AND CONCLUSION	23
9.	REFERENCES	24

LIST OF APPENDICES

APPENDIX 1 FIGURES AND SUMMARY TABLES

APPENDIX 2 INDIVIDUAL DATA TABLES

APPENDIX 3 PHASE REPORT FORMULATION ANALYSIS

APPENDIX 4 PHASE REPORT HISTOPATHOLOGY

APPENDIX 5 SUMMARY OF DOSE RANGE FINDING STUDY

APPENDIX 6 CERTIFICATE OF PURITY

1. STATEMENT OF GLP COMPLIANCE

Charles River Den Bosch, 's-Hertogenbosch, The Netherlands

All phases of this study performed by the test facility were conducted in compliance with:

- OECD Principles of Good Laboratory Practice.
- EC Council Directive 2004 (2004/10/EC, February 11, 2004, Official Journal of February 20, 2004).

Except for the following:

- Trial formulation preparation (for optimal vehicle selection) had a non-GLP status but was carried out in the quality assured environment of Charles River Den Bosch GLP test facility.

The data generated and reported are considered to be valid.

Charles River Den Bosch

Signature: 

Name: J.E.H.M. Latour, MSc.

Title: Study Director

Date: 03 March 2017

2. TEST FACILITY QUALITY ASSURANCE STATEMENT

Charles River Den Bosch, 's-Hertogenbosch, The Netherlands.

Study title: Repeated dose 28-day oral toxicity study with MLA-3202 via daily gavage in the rat.

This report was inspected by the Charles River Den Bosch Quality Assurance Unit (QAU) according to the Standard Operating Procedure(s).

The reported method and procedures were found to describe those used and the report reflects the raw data.

During the on-site process inspections, procedures applicable to this type of study were inspected.

The dates of Quality Assurance inspections are given below.

Test Facility Study No. 514867

Type of Inspections	Phase/Process	Start Inspection date	End Inspection date	Reporting date to TFM and SD*
Study	Study Plan	13-Sep-2016	13-Sep-2016	13-Sep-2016
	Study Plan Amendment 01	03-Oct-2016	03-Oct-2016	03-Oct-2016
	Exposure	19-Oct-2016	19-Oct-2016	19-Oct-2016
	Study Plan Amendment 02	20-Oct-2016	20-Oct-2016	20-Oct-2016
	Study Plan Amendment 03	15-Dec-2016	15-Dec-2016	15-Dec-2016
	Report	22-Feb-2017	24-Feb-2017	24-Feb-2017
	Study Plan Amendment 04	28-Feb-2017	28-Feb-2017	28-Feb-2017
	Study Plan Amendment 05	01-Mar-2017	01-Mar-2017	01-Mar-2017
Process	Test Item Receipt	22-Aug-2016	02-Sep-2016	09-Sep-2016
	Test Item Handling			
Analytical and physical chemistry		05-Sep-2016	22-Sep-2016	30-Sep-2016
	Test Item Handling			
	Exposure			
	Observations/Measurements			
	Specimen Handling			
Histology		12-Sep-2016	19-Sep-2016	20-Sep-2016
	Specimen Handling			
Necropsy		12-Sep-2016	19-Sep-2016	20-Sep-2016
	Observations/Measurements			
	Specimen Handling			
Animal Facilities		10-Oct-2016	21-Oct-2016	21-Oct-2016
	Test Item Handling			
	Exposure			
	Observations/Measurements			
	Specimen Handling			

Clinical pathology	07-Nov-2016	10-Nov-2016	10-Nov-2016
Observations/Measurements			
Specimen Handling			
 Test Item Formulation	08-Nov-2016	22-Nov-2016	23-Nov-2016
Test Item Handling			

*TFM=Test Facility Management SD = Study Director

The facility inspection program is conducted in accordance with Standard Operating Procedure.

The review of the final report was completed on the date of signing this QA statement.

Charles River Den Bosch

Signature: *U. Wiets*

Name: **Ulrich Wiets**
Quality Assurance Auditor

Date: *03 March 2017*

3. SUMMARY

Title

Repeated dose 28-day oral toxicity study with MLA-3202 via daily gavage in the rat.

Guidelines

The study was based on the following guidelines:

- EC No 440/2008, B.7 Repeated Dose (28 days) Toxicity (oral), 2008.
- OECD 407, Repeated Dose 28-day Oral Toxicity Study in Rodents, 2008.
- OPPTS 870.3050, Repeated dose 28-day oral toxicity study in rodents. Office of Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-00-366, 2000.

Rationale for dose levels

Based on the results of a 5-day range finding study (Test Facility Study No. 514938; See [APPENDIX 5](#)), the dose levels for this 28-day oral gavage study were selected to be 0, 100, 300 and 1000 mg/kg.

Study outline

The test item, formulated in water, was administered daily for 28 days via oral gavage to SPF-bred Wistar rats. One control group and three treated groups were tested, each consisting of 5 males and 5 females.

Chemical analyses of formulations were conducted once during the study to assess accuracy and homogeneity.

The following parameters were evaluated: clinical signs daily; functional observation tests in Week 4; body weight and food consumption weekly; clinical pathology and macroscopy at termination; organ weights and histopathology on a selection of tissues.

Results

Formulation analyses confirmed that formulations of test item in water were prepared accurately and homogenously.

No adverse treatment-related effects were seen in any of the dose levels tested. In addition, there were no toxicologically significant changes observed in parameters including clinical appearance, motor activity, functional observations, and macroscopic examination.

Microscopic examination revealed absence of the normally occurring hematopoiesis observed in the spleens of 1000 mg/kg males, which correlated with reduced spleen weight. However, in the absence of any other indicator of toxicity (for example haematology parameters), these spleen findings were considered non-adverse. The minimal hepatocellular hypertrophy of the liver seen in 1000 mg/kg females was accompanied by increased liver weight, as well as changes in alanine aminotransferase levels and cholesterol, liver-related biochemical parameters. However, in the absence of any degenerative findings in the liver, these effects were considered to be non-adverse.

Other test item-related findings include a slightly reduced bodyweight gain in 1000 mg/kg males supported by a slightly reduced food intake. In contrast females showed a slightly increased body weight gain. Without a clear dose response or any corroborative findings these changes small changes in body weights were considered not adverse.

Conclusion

From the results presented in this report, a No Observed Adverse Effect Level (NOAEL) of 1000 mg/kg was established for MLA-3202.

4. INTRODUCTION

4.1. Study Schedule

Experimental starting date	19 September 2016 (allocation dose range finding study: see APPENDIX 5)
Treatment	14 October 2016 to 10 November 2016
Clinical Pathology	11 November 2016
Necropsy	11 November 2016
Experimental completion date	11 November 2016 (end of in-life phase)

Test item preparation and sampling, all animal activities and necropsy were performed at the Schaijk location. All other activities, including the dose range finding study, were performed at the 's-Hertogenbosch location.

4.2. Purpose

The nature and purpose of this toxicity study was to assess the toxic potential of the test item when administered to rats via daily oral gavage for a period of 28 days.

A No Observed Adverse Effect Level (NOAEL) was evaluated.

This study should provide a rational basis for toxicological risk assessment in man. The oral route was selected as it is a possible route of human exposure during manufacture, handling or use of the test item.

4.3. Guidelines

This type of study plan was reviewed and agreed by the Laboratory Animal Welfare Officer and the Ethical Committee (DEC 14-59) as required by the Dutch Act on Animal Experimentation (February 1997).

The study procedures described in this report were in compliance with the following guidelines:

- Commission regulation (EC) No 440/2008 Part B: Methods for the Determination of Toxicity and other Health Effects; B.7: "Repeated Dose (28 days) Toxicity (oral)". Official Journal of the European Union No. L142, May 2008.
- Organization for Economic Co-operation and Development (OECD), OECD Guidelines for Testing of Chemicals, Section 4, Health Effects, No. 407: "Repeated Dose 28-day Oral Toxicity Study in Rodents", Paris, 03 October 2008.
- United States Environmental Protection Agency (EPA). Health Effects Test Guidelines, OPPTS 870.3050, Repeated dose 28-day oral toxicity study in rodents. Office of Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-00-366, July 2000.

4.4. Retention of Records and Materials

Records and material pertaining to the study, which include the study plan and amendments, raw data, specimens, except perishable specimens, and the final report will be retained in the archives of the test facility for a minimum of 5 years after the finalization of the report. After this period, the Sponsor will be contacted to determine how the records and materials should be handled. The test facility will retain information concerning decisions made.

Perishable specimens (e.g. requiring refrigeration or freezing) will be discarded following evaluation in the study without further notice to the study Sponsor.

A sample of the test item will be retained until expiry date or applicable retest date. After this period the sample(s) will be destroyed.

4.5. Responsible Personnel

4.5.1. Test Facility

Study Director	J.E.H.M. Latour, MSc. Tel: +31 73 640 6700 Fax: +31 73 640 6799 Email: judith.latour@crl.com
Coordinating Biotechnician	M.M.A. Rijkers (Charles River Den Bosch) (Main study)
Clinical Pathology	P.L.J. Polman, BSc. (Charles River Den Bosch)
Analytical Chemistry	M.J.C. Brekelmans, MSc. (Principal Scientist, Charles River Den Bosch)
Necropsy	M. Schelling (Charles River Den Bosch)
Histotechnology	W. Verhoef (Charles River Den Bosch)
Histopathology	J.F.M. Lensen, PhD., CRP/TP (Principal Scientist, Charles River Den Bosch)
QA	C.J. Mitchell, BSc. (Charles River Den Bosch) Email: christine.mitchell@crl.com
Test facility Management Representative	H.H. Emmen, MSc. (Charles River Den Bosch) Email: harry.emmen@crl.com

4.5.2. Sponsor Representative

Study Monitor	Audrey Batoon, Ph.D.
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4.5.3. Data Collection

Three Test Facility Study numbers were used to collect online data. All data were reported under Test Facility Study No. 514867.

Test Facility Study No.	Online data
514938	Dose Range finding Study
514939	Arena observations
514867	All other data

5. MATERIALS AND METHODS

5.1. Test Item

5.1.1. Test Item Information

Test item	207258/A
Identification	MLA-3202
Appearance	Clear amber-red liquid
Batch	RC-1045
Purity/Composition	UVCB
Test item storage	At room temperature
Stable under storage conditions until	17 February 2019 (expiry date)

5.1.2. Study Specific Item Information

Chemical name (IUPAC), synonym or trade name	Amides, tallow, N,N-bis(2-hydroxypropyl)
CAS Number	1454803-04-3
pH	6-7
Specific gravity/density	0.9394
Solubility in vehicle:	< 1 g/L
• Water	
Stability in vehicle:	Stability for at least 6 hours at room temperature, under normal laboratory light conditions over the concentration range 1 to 200 mg/mL and in a refrigerator for at least 8 days, Project 514869.
• Water	

5.2. Vehicle Information

Vehicle	Water (Elix, Millipore S.A.S., Molsheim, France).
Rationale for vehicle	Based on trial formulations performed at Charles River Den Bosch and on information from the Sponsor.

5.3. Test Item Preparation

Method of formulation	Formulations (w/w) were prepared daily within 6 hours prior to dosing and were homogenized to a visually acceptable level. Adjustment was made for specific gravity of the test item. No correction was made for the purity/composition of the test item.
Storage conditions	At room temperature.

5.4. Chemical Analysis of Dose Preparations

Analyses were conducted on a single occasion during the treatment phase, according to a validated method (Test Facility Study No. 514869). Samples of formulations were analyzed for homogeneity (highest and lowest concentration) and accuracy of preparation (all concentrations).

The accuracy of preparation was considered acceptable if the mean measured concentrations were 85-115% of the target concentration for suspensions. Homogeneity was demonstrated if the coefficient of variation was $\leq 10\%$. Formulations were considered stable if the relative difference before and after storage was maximally 10%.

5.5. Test System

Test system	Rat: Crl:WI(Han) (outbred, SPF-Quality).
Rationale	Recognized by international guidelines as the recommended test system (e.g. EPA, FDA, OECD and EC).
Source	Charles River Deutschland, Sulzfeld, Germany.
Total number of animals	20 males, 20 females (females were nulliparous and non-pregnant).
Age at start of treatment	Approximately 6 weeks.
Identification	Earmark and tattoo.
Randomization	By computer-generated random algorithm according to body weight, with all animals within $\pm 20\%$ of the sex mean.
Acclimatization period	At least 5 days before the start of treatment under laboratory conditions.
Health inspection	Upon receipt of the animals.

5.6. Allocation

Group	Dose level ¹ mg/kg	Dose volume mL/kg	Number of animals		Animal numbers	
			Males	Females	Males	Females
1	0 (vehicle)	5	5	5	1-5	21-25
2	100	5	5	5	6-10	26-30
3	300	5	5	5	11-15	31-35
4	1000	5	5	5	16-20	36-40

¹ Dose levels are based on results of a 5-day dose range finding study with MLA-3202 (Test Facility Study No. 514938). A summary of the results is included in this report (see APPENDIX 5).

5.7. Animal Husbandry

Room number	MR1222 (MR1221B for motor activity measurements).
Conditions	Environmental controls for the animal room were set to maintain 18 to 24°C, a relative humidity of 40 to 70%, at least 10 air changes/hour, and a 12-hour light/12-hour dark cycle. The light/dark cycle was interrupted for study related activities. Any variations to these conditions were evaluated and maintained in the raw data.
Accommodation	Group housing of 5 animals per sex in Macrolon cages (MIV type, height 18 cm) with sterilized sawdust as bedding material (Lignocel S 8-15, JRS - J.Rettenmaier & Söhne GmbH + CO. KG, Rosenberg, Germany) and paper as cage-enrichment (Enviro-dri, Wm. Lilico & Son (Wonham Mill Ltd), Surrey, United Kingdom). During locomotor activity monitoring, animals were housed individually in a Hi-temp polycarbonate cage (Ancare corp., USA; dimensions: 48.3 x 26.7 x 20.3 cm) without cage-enrichment, bedding material, food and water.
Diet	Free access to pelleted rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany). During motor activity measurements, animals did not have access to food for a maximum of 2 hours.
Water	Free access to tap water.

Diet, water, bedding and cage enrichment evaluation for contaminants and/or nutrients was performed according to facility standard procedures. There were no findings that could interfere with the study.

5.8. Treatment

Method	Oral gavage, using a plastic feeding tube. Formulations were placed on a magnetic stirrer during dosing. The dose control system (DCS) was used to verify the dosing procedure.
Dose volume	5 mL/kg body weight. Actual dose volumes were calculated weekly according to the latest body weight.
Frequency	Once daily, 7 days per week, approximately the same time each day with a maximum of 6 hours difference between the earliest and latest dose.
Duration of treatment	At least 28 days. Animals were dosed up to the day prior to necropsy.

5.9. Observations

Mortality / Viability	At least twice daily.
Clinical signs	<p>At least once daily from start of treatment onwards, detailed clinical observations were made in all animals immediately (0-15 minutes) after dosing (no peak effect of occurrence of clinical signs was observed in the dose range finding study (Test Facility Study No. 514938)).</p> <p>Once prior to start of treatment and at weekly intervals, this was also performed outside the home cage in a standard arena (collected under Test Facility Study No. 514939 for logistic reasons and reported under Test Facility Study No. 514867). The time of onset, grade and duration of any observed signs were recorded. Signs were graded for severity and the maximum grade was predefined at 3 or 4. Grades were coded as slight (grade 1), moderate (grade 2), severe (grade 3) and very severe (grade 4). For certain signs, only its presence (grade 1) or absence (grade 0) was scored. In the data tables, the scored grades are reported, as well as the percentage of animals affected in summary tables.</p>
Functional Observations	<p>During Week 4 of treatment, functional observation tests were performed on all animals. Tests were performed after dosing at no specific time point, but within a similar time period after dosing (based on the absence of a peak effect in occurrence of clinical signs in the dose range finding study (Test Facility Study No. 514938)).</p> <p>The following tests were performed (abbreviations mentioned in the respective tables indicated between brackets):</p> <ul style="list-style-type: none">• Hearing ability (HEARING), pupillary reflex (PUPIL L/R), static righting reflex (STATIC R) (Score 0 = normal/present, score 1 = abnormal/absent).• Fore- and hind-limb grip strength, recorded as the mean of three measurements per animal (Series M4-10, Mark-10 Corporation, J.J. Bos, Gouda, The Netherlands).• Locomotor activity (recording period: 1-hour under normal laboratory light conditions, using a computerized monitoring system, Kinder Scientific LLC, Poway, USA). Total movements and ambulations are reported. Ambulations represent movements characterized by a relocation of the entire body position like walking, whereas total movements represent all movements made by the animals, including ambulations but also smaller or more fine movements like grooming, weaving or movements of the head.
Body weights	Weekly.
Food consumption	Weekly.

Water consumption Subjective appraisal was maintained during the study, but no quantitative investigation introduced as no effect was suspected.

5.10. Clinical Laboratory Investigations

Blood samples were collected under anaesthesia using isoflurane (Abbott B.V., Hoofddorp, The Netherlands) between 7.00 and 10.30 a.m. at the end of the treatment. Animals were deprived of food overnight (for a maximum of 24 hours), but water was available. Blood samples were drawn from the retro-orbital sinus and collected into tubes (Greiner Bio-One GmbH, Kremsmünster, Austria) prepared with K₃-EDTA for haematological parameters (0.5 mL), with citrate for clotting tests (0.45 mL) and Li-heparin treated tubes for clinical biochemistry parameters (0.5 mL). An additional blood sample (0.25 mL) was collected into serum tubes for determination of bile acids. The following parameters were determined:

Parameter	Abbreviation	Unit
<i>Haematology^a</i>		
White blood cells	WBC	10 ⁹ /L
Differential leucocyte count		% WBC
neutrophils, lymphocytes, monocytes, eosinophils, basophils		
Red blood cells		10 ¹² /L
Reticulocytes		% RBC
Red blood cell distribution width	RDW	%
Haemoglobin		mmol/L
Haematocrit		L/L
Mean corpuscular volume	MCV	fL
Mean corpuscular haemoglobin	MCH	fmol
Mean corpuscular haemoglobin concentration	MCHC	mmol/L
Platelets		10 ⁹ /L
<i>Clotting Potential^b</i>		
Prothrombin time	PT	s
Activated Partial thromboplastin time	APTT	s
<i>Clinical Biochemistry^c</i>		
Alanine aminotransferase	ALAT	U/L
Aspartate aminotransferase	ASAT	U/L
Alkaline phosphatase	ALP	U/L
Total Protein		g/L
Albumin		g/L
Total Bilirubin		µmol/L
Urea		mmol/L
Creatinine		µmol/L
Glucose		mmol/L
Cholesterol		mmol/L
Sodium		mmol/L
Potassium		mmol/L
Chloride		mmol/L
Calcium		mmol/L
Inorganic Phosphate	Inorg. Phos	mmol/L
Bile acids		µmol/L

^a Instrumentation: ADVIA® 2120i (Siemens Healthcare Diagnostics B.V., Den Haag, The Netherlands).

^b Instrumentation: STA Compact (Diagnostica Stago S.A.S., Asnières, France).

^c Instrumentation: Olympus AU400 (Beckman Coulter Nederland B.V., Woerden, The Netherlands).

5.11. Pathology

5.11.1. Necropsy

On the scheduled day of necropsy, animals were deeply anaesthetized using isoflurane (Abbott B.V., Hoofddorp, The Netherlands) and subsequently exsanguinated and subjected to a full *post mortem* examination. Animals were deprived of food overnight (with a maximum of 24 hours) prior to scheduled necropsy. All animals assigned to the study were necropsied and descriptions of all macroscopic abnormalities recorded. Samples of the following tissues and organs were collected from all animals at necropsy and fixed in 10% buffered formalin (neutral phosphate buffered 4% formaldehyde solution, Klinipath, Duiven, The Netherlands):

Identification marks: not processed	Ovaries
Adrenal glands	(Pancreas)
(Aorta)	Peyer's patches [jejunum, ileum] if detectable
Brain [cerebellum, mid-brain, cortex]	(Pituitary gland)
Caecum	(Preputial gland)
Cervix	Prostate gland
(Clitoral gland)	Rectum
Colon	(Salivary glands - mandibular, sublingual)
Duodenum	Sciatic nerve
Epididymides *	Seminal vesicles including coagulating gland
Eyes (including optic nerve and harderian gland) *	Skeletal muscle
(Female mammary gland area)	(Skin)
Femur including joint	Spinal cord -cervical, midthoracic, lumbar
Heart	Spleen
Ileum	Sternum with bone marrow
Jejunum	Stomach
Kidneys	Testes *
(Larynx)	Thymus
(Lacrimal gland, exorbital)	Thyroid including parathyroid [if detectable]
Liver	(Tongue)
Lung, infused with formalin	Trachea
Lymph nodes - mandibular, mesenteric	Urinary bladder
(Nasopharynx)	Uterus
(Oesophagus)	Vagina
	All gross lesions

* Fixed in modified Davidson's solution, prepared at Charles River Den Bosch using Formaldehyde 37-40%, Ethanol, Acetic acid - glacial (all Merck, Darmstadt, Germany) and Milli-Ro water (Millipore Corporation, Bedford, USA). Tissues were transferred to formalin after fixation for at least 24 hours.

Tissues/organs mentioned in parentheses were not examined by the pathologist, since no signs of toxicity were noted at macroscopic examination.

5.11.2. Organ Weights

The following organ weights (and terminal body weight) were recorded from the animals on the scheduled day of necropsy:

Adrenal glands	Spleen
Brain	Testes
Epididymides	Thymus
Heart	Uterus (including cervix)
Kidneys	Prostate
Liver	Seminal vesicles including coagulating glands
Ovaries	Thyroid including parathyroid

5.11.3. Histotechnology

All organ and tissue samples, as defined under Histopathology (following), were processed, embedded in paraffin wax (Klinipath, Duiven, The Netherlands), cut at a thickness of 2-4 micrometers and stained with haematoxylin and eosin (Klinipath, Duiven, The Netherlands).

5.11.4. Histopathology

The following slides were examined by a pathologist:

- all tissues collected at the scheduled sacrifice from all Group 1 and 4 animals,
- spleens of all male animals of Groups 2 and 3 and livers of female animals of Groups 2 and 3, based on (possible) treatment-related changes in these organs in Group 4,
- all gross lesions.

All abnormalities were described and included in the report. An attempt was made to correlate gross observations with microscopic findings.

Histopathology was subjected to a peer review.

5.12. Interpretation

The following statistical methods were used to analyze the data:

- If the variables could be assumed to follow a normal distribution, the Dunnett-test (Ref. 1; many-to-one t-test) based on a pooled variance estimate was applied for the comparison of the treated groups and the control groups for each sex.
- The Steel-test (Ref. 2; many-to-one rank test) was applied if the data could not be assumed to follow a normal distribution.
- The Fisher Exact-test (Ref. 3) was applied to frequency data.
- The Kruskal-Wallis nonparametric ANOVA test (Ref. 4) was applied to motor activity data to determine intergroup differences. In case intergroup differences were seen, the Wilcoxon test (Ref. 5) was applied to compare the treated groups to the control group.

All tests were two-sided and in all cases $p < 0.05$ was accepted as the lowest level of significance. Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables. Test statistics were calculated on the basis of exact values for means and pooled variances. Individual values, means and standard deviations may have been rounded off before printing. As a result, two groups may display the same printed means for a given parameter, yet display different test statistics values.

5.13. List of Deviations**5.13.1. List of Study Plan Deviations**

1 The dosing control system was used during the first week of study, although this was not noted in the study plan. The amendment for the use of the dosing control system was added to the study plan in the second week of study.

Evaluation: The dosing control system is standardly used in repeated dose toxicity studies as an extra check during dosing. It was therefore considered have positively affected the study integrity.

2 The rectum of animal no. 1 and spinal cord of animal no. 25 were not available for histopathology. Reasons included the possibility that these tissues were not discernable at necropsy or trimming, or were erroneously not collected at necropsy.

Evaluation: Sufficient data was available for evaluation.

No Study Plan deviation was observed during the range finding study (Test Facility Study No. 514938).

The study integrity was not adversely affected by the deviations.

5.13.2. List of Standard Operating Procedures Deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

6. ELECTRONIC SYSTEMS FOR DATA ACQUISITION

Observations/measurements in the study were recorded electronically using the following programme(s):

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA): Environmental monitoring.
- TOXDATA version 8.0 (Charles River Den Bosch, 's-Hertogenbosch, The Netherlands): Mortality / Clinical signs / Functional Observations (hearing ability, pupillary reflex and static righting reflex) / Body weights / Food consumption / Organ weights.
- MotorMonitor II version 15251-16GLP (Kinder Scientific LLC, Poway, USA): Motor activity measurement.
- ADVIA® 2120i Hematology System version 6.3.2-MS (Siemens Healthcare Diagnostics B.V., Den Haag, The Netherlands): Haematology.
- STA Compact® version 107.07 (Diagnostica Stago S.A.S., Asnières, France): Clotting parameters.
- AU 400 version 9.1 (Beckman Coulter Nederland B.V., Woerden, The Netherlands): Clinical biochemistry.
- Pathdata version 6.2e2 (Pathology Data Systems, Basel, Switzerland): Histopathology.
- DCS Client application version 1.0.6, Server application version 1.0.6. and DCS Smart client version 1.0.6 (OCS Consulting , 's-Hertogenbosch, The Netherlands): dosing control.
- Empower3 database version 7.21 (Waters, Milford, MA, USA): Formulation analysis.

7. RESULTS

For further details on summary data, see [APPENDIX 1](#) and on individual data, see [APPENDIX 2](#).

7.1. Analysis of Dose Preparations

The concentrations analysed in the formulations of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%).

No test item was detected in the Group 1 formulation.

The formulations of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation $\leq 10\%$).

For further details on formulation analysis, see [APPENDIX 3](#).

7.2. Observations

7.2.1. Mortality

No mortality occurred during the study period.

7.2.2. Clinical Signs

No toxicologically relevant clinical signs were noted during daily detailed clinical observations or during weekly arena observations.

Salivation was noted after dosing for the test item treated animals showing a dose related trend but was not considered toxicologically relevant, taking into account the nature and minor severity of the effect and its time of occurrence (i.e. after dosing). This sign was considered to be a physiological response related to taste of the test item rather than a sign of systemic toxicity.

Other clinical signs noted during the treatment period occurred within the range of background findings to be expected for rats of this age and strain which are housed and treated under the conditions in this study and did not show any apparent dose-related trend. At the incidence observed, these were considered to be unrelated to treatment.

7.2.3. Functional Observations

Hearing ability, pupillary reflex and static righting reflex were normal in all examined animals. Grip strength and motor activity was similar between treated and control groups. All groups showed a similar motor activity habituation profile with a decreasing trend in activity over the duration of the test period.

There was a slight tendency for reduced hindgrip strength and increased foregrip strength in high dose animals, however this effect is not statistically significant and was not supported by clinical observations or other functional observation changes, and had no supportive neuro-morphological correlates. Therefore it was considered not toxicologically relevant.

7.2.4. Body Weight

Body weight and body weight gain were statistically significantly reduced in 1000 mg/kg males from Day 8 onwards but the change was only slight and without a clear dose response.

In 1000 mg/kg females, body weight gain was statistically significantly increased on an intermittent basis throughout the study and 300 mg/kg females show an increased body weight gain after 2 weeks of treatment only.

7.2.5. Food Consumption

Slightly reduced absolute and relative food consumption, was seen in males treated at 1000 mg/kg without a clear dose response.

In females, absolute and relative food consumption before or after correction for body weight remained similar to the control level over the study period.

7.3. Clinical Laboratory Investigations

7.3.1. Haematology

No toxicologically relevant changes were noted in haematological parameters.

Any statistically significant changes in haematology parameters were considered to be unrelated to treatment as these occurred in the absence of a dose-related trend.

7.3.2. Clinical Biochemistry

Alanine aminotransferase (ALAT) and cholesterol levels were statistically significantly increased at 1000 mg/kg in both sexes.

Calcium levels were significantly increased at 1000 mg/kg in males but in the absence of corroborative findings were considered not toxicologically relevant also taking into account the slight nature of the change.

Any other statistically significant changes in clinical biochemistry parameters were considered to be unrelated to treatment as these occurred in the absence of a dose-related trend.

7.4. Pathology

7.4.1. Macroscopic Examination

There were no test item-related gross observations.

All of the recorded macroscopic findings were within the range of background gross observations encountered in rats of this age and strain.

7.4.2. Organ Weights

Test item-related lower spleen weights (absolute -24% compared to control) were noted in the 1000 mg/kg males and higher liver weights (absolute 24%; relative 19% compared to control) were noted in the 1000 mg/kg females.

For males, the other organ weights were in line with the decrease in body weight.

There were no other test item-related organ weight changes.

7.4.3. Microscopic Examination

Test item-related microscopic findings were noted in the spleen of the 1000 mg/kg group males and the liver of the 1000 mg/kg females.

Dose level (mg/kg):	Males			
	0	100	300	1000
SPLEEN ^a	5	5	5	5
<i>Extramedullary hematopoiesis</i>				
Minimal	5	4	3	-
Slight	-	1	-	-
LIVER ^a	5	5	5	5
<i>Hepatocellular hypertrophy</i>				
Minimal	-	-	-	4

^a = Number of tissues examined from each group.

In the spleen, the normally occurring extramedullary hematopoiesis was not detectable in males treated at 1000 mg/kg.

Hepatocellular hypertrophy of the liver was present in females treated at 1000 mg/kg at minimal degree.

The remainder of the recorded microscopic findings were within the range of background pathology encountered in rats of this age and strain. There were no test item-related alterations in the prevalence, severity, or histological character of those incidental tissue alterations.

For further details on histopathology, see [APPENDIX 4](#).

8. DISCUSSION AND CONCLUSION

Wistar rats were treated with MLA-3202 for 28 consecutive days via oral gavage at dose levels of 100, 300 and 1000 mg/kg.

Formulation analyses confirmed that formulations of test item in water were prepared accurately and homogenously.

No adverse treatment-related effects were seen in any of the dose levels tested. In addition, there were no toxicologically significant changes observed in parameters including clinical appearance, motor activity, functional observations, and macroscopic examination.

Microscopic examination revealed absence of the normally occurring hematopoiesis observed in the spleens of 1000 mg/kg males, which correlated with reduced spleen weight. However, in the absence of any other indicator of toxicity (for example haematology parameters), these spleen findings were considered non-adverse. The minimal hepatocellular hypertrophy of the liver seen in 1000 mg/kg females was accompanied by increased liver weight, as well as changes in alanine aminotransferase levels and cholesterol, liver-related biochemical parameters. However, in the absence of any degenerative findings in the liver, these effects were considered to be non-adverse ([Ref. 6](#)).

Other test item-related findings include a slightly reduced bodyweight gain in 1000 mg/kg males together with a slight reduction in food intake in 1000 mg/kg males. In contrast females showed a slightly increased body weight gain. Without a clear dose response or any corroborative findings these small changes in body weights were considered not adverse.

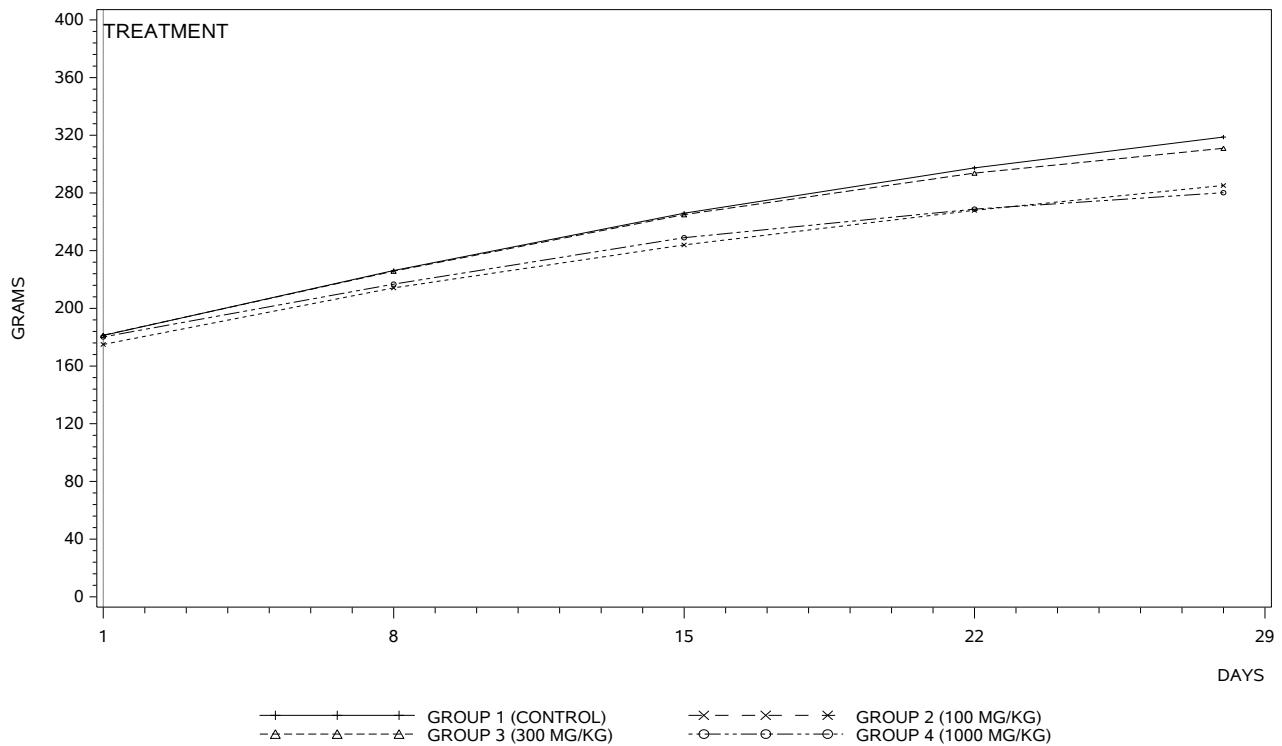
From the results presented in this report, a No Observed Adverse Effect Level (NOAEL) of 1000 mg/kg was established for MLA-3202.

9. REFERENCES

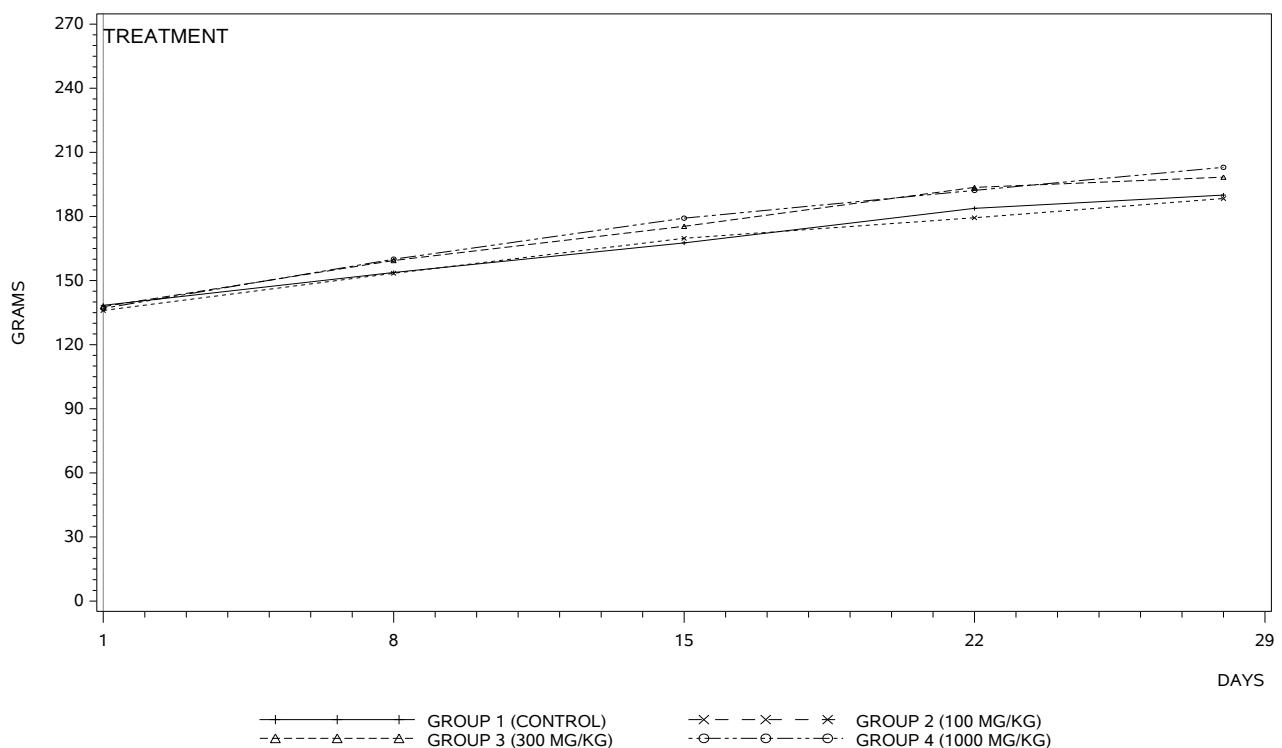
- Ref. 1 C.W. Dunnett, A Multiple Comparison Procedure for Comparing Several Treatments with a Control, *J. Amer. Stat. Assoc.* 50, 1096-1121 (1955).
- Ref. 2 R.G. Miller, *Simultaneous Statistical Inference*, Springer Verlag, New York (1981).
- Ref. 3 R.A. Fisher, *Statistical Methods for Research Workers*, Oliver and Boyd, Edinburgh (1950).
- Ref. 4 Kruskal W.H. and Wallis W.A. Use of ranks in one-criterion variance analysis. *Journal of the American Statistical Association* 47 (260): 583-621, December (1952).
- Ref. 5 Wilcoxon, F. Individual comparisons by ranking methods. *Biometrics*, 1, 80-83 (1945).
- Ref. 6 Kerlin, R., Bolon, B., Burkhardt, J., Francke, S., Greaves, P., Meador, V., Popp, P. (2016). Scientific and Regulatory Policy Committee: Recommended (“Best”) Practice for Determining, Communicating, and Using Adverse Effect Data from Nonclinical Studies. *Toxicol. Pathol.* 44(2), 147-162.

APPENDIX 1
FIGURES AND SUMMARY TABLES

1.1 BODY WEIGHTS (GRAM) MALES

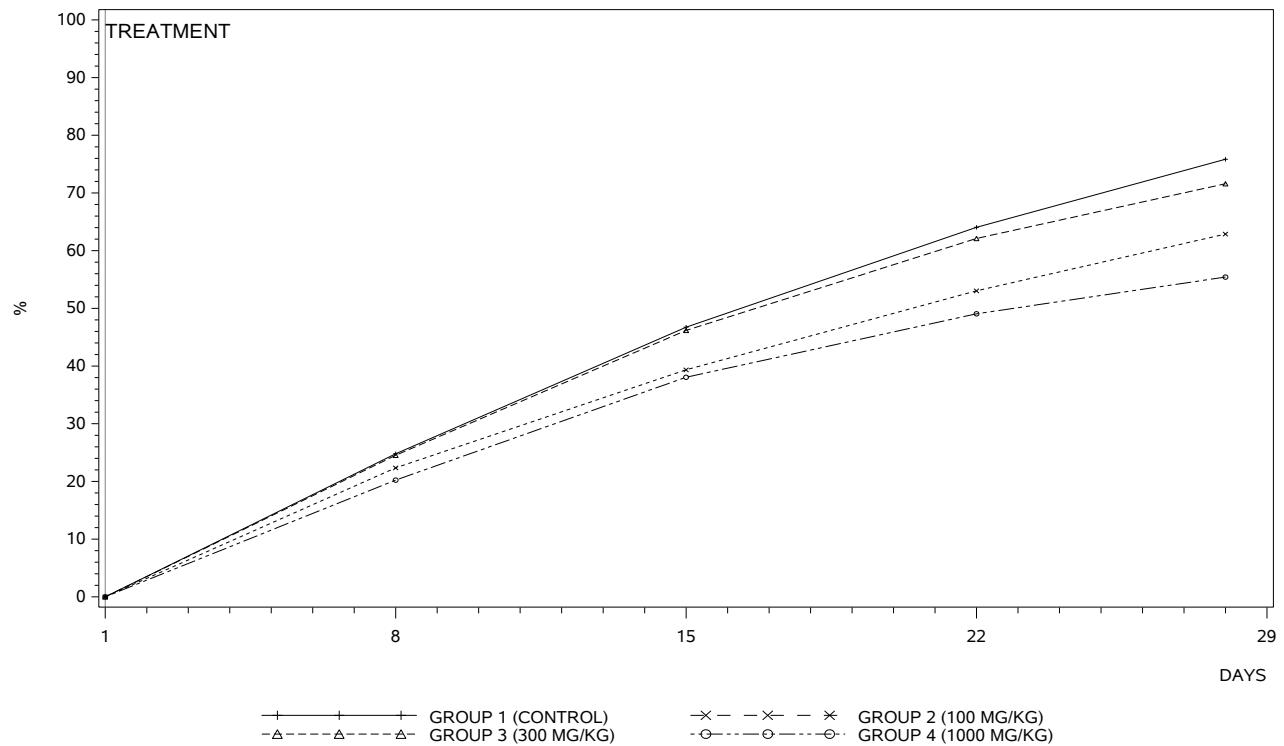


1.1 BODY WEIGHTS (GRAM) FEMALES

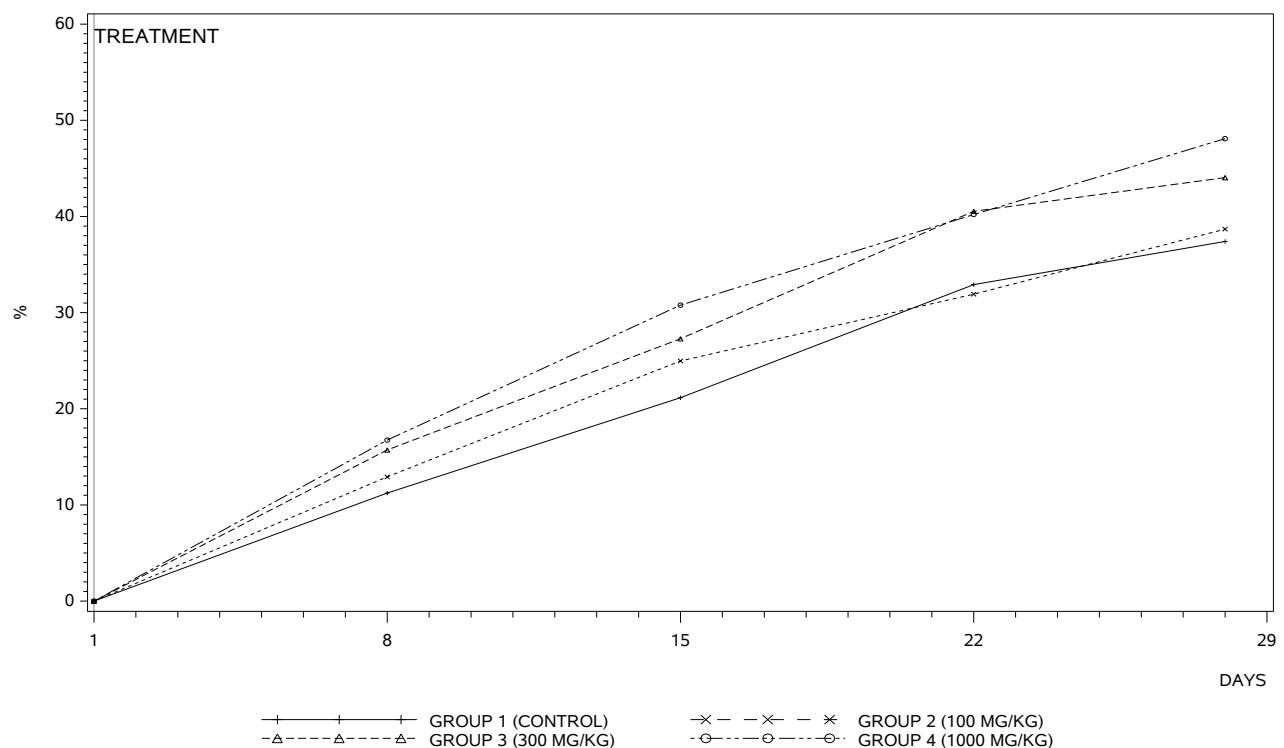


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1.2 BODY WEIGHT GAIN (%) MALES

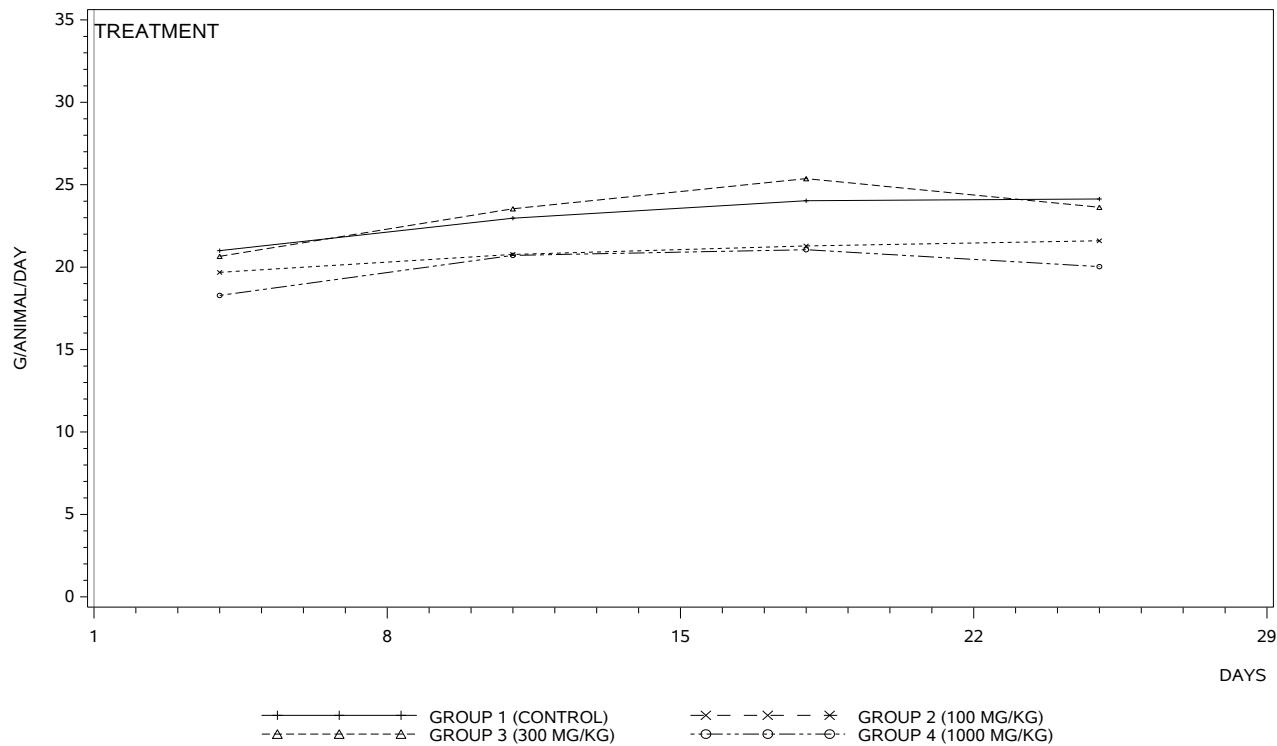


1.2 BODY WEIGHT GAIN (%) FEMALES

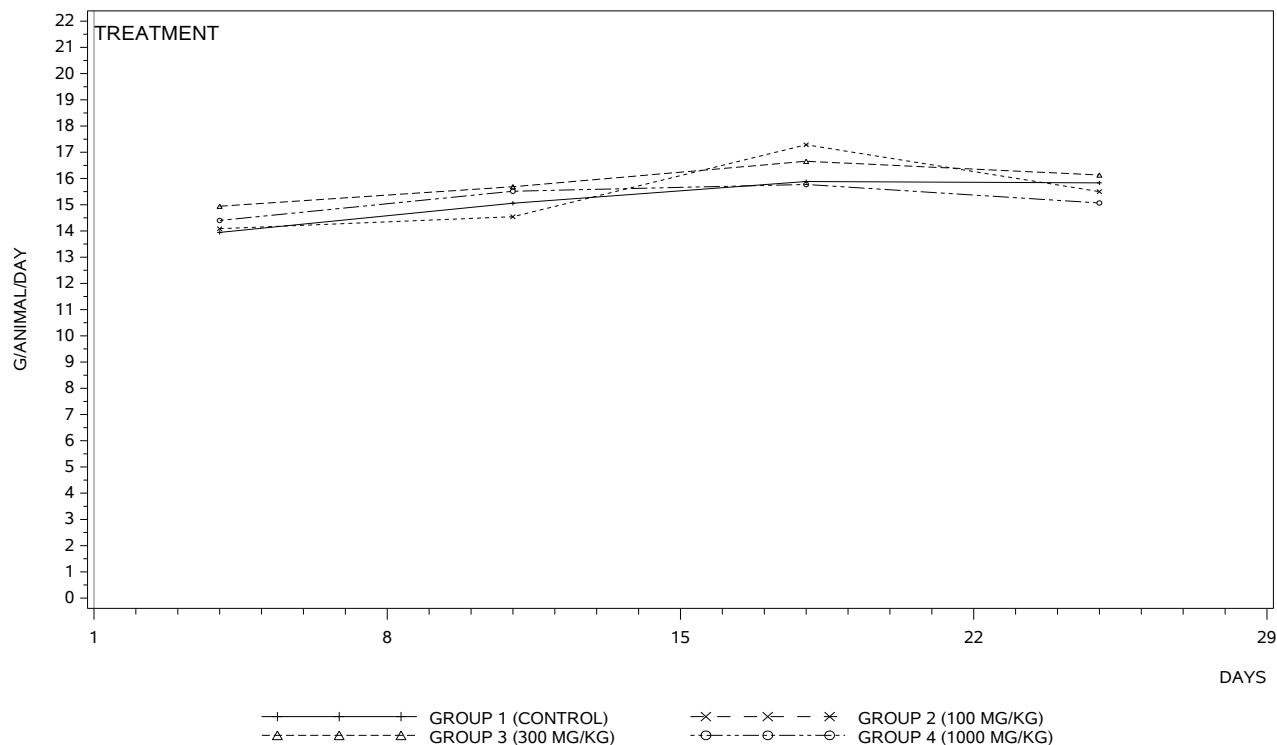


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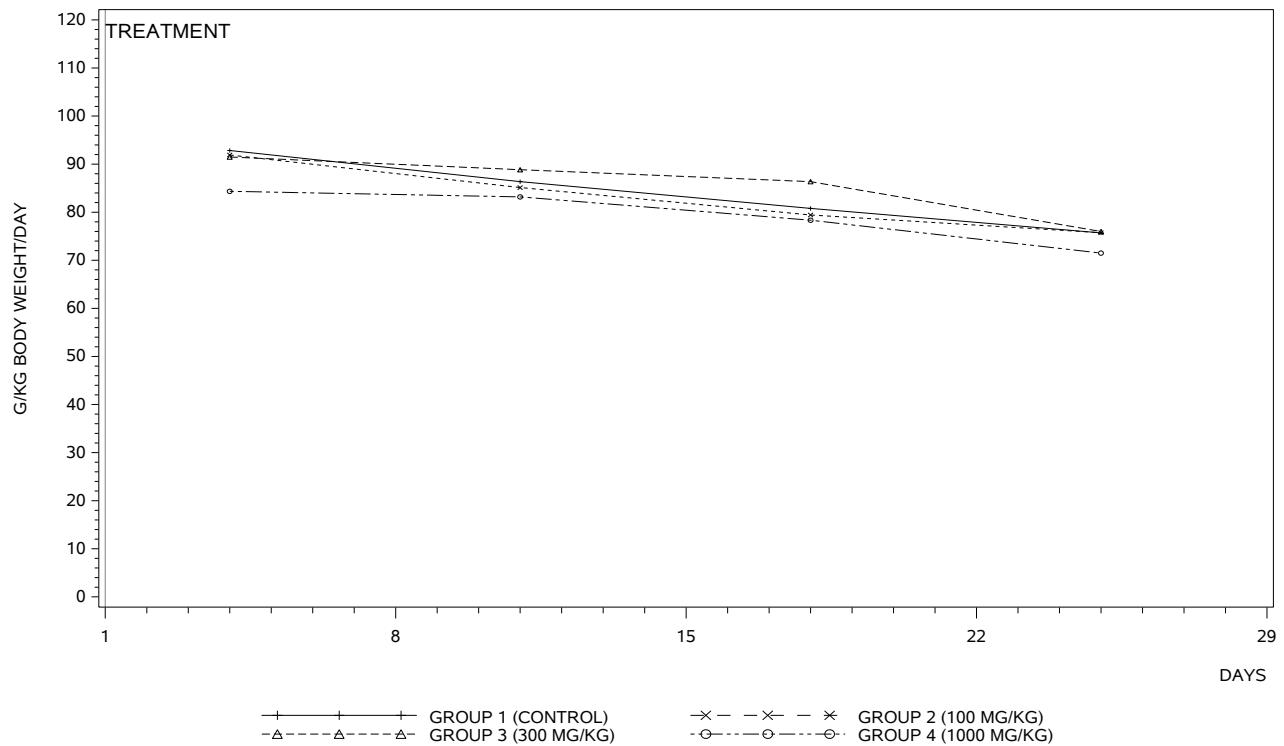
1.3 FOOD CONSUMPTION (G/ANIMAL/DAY) MALES



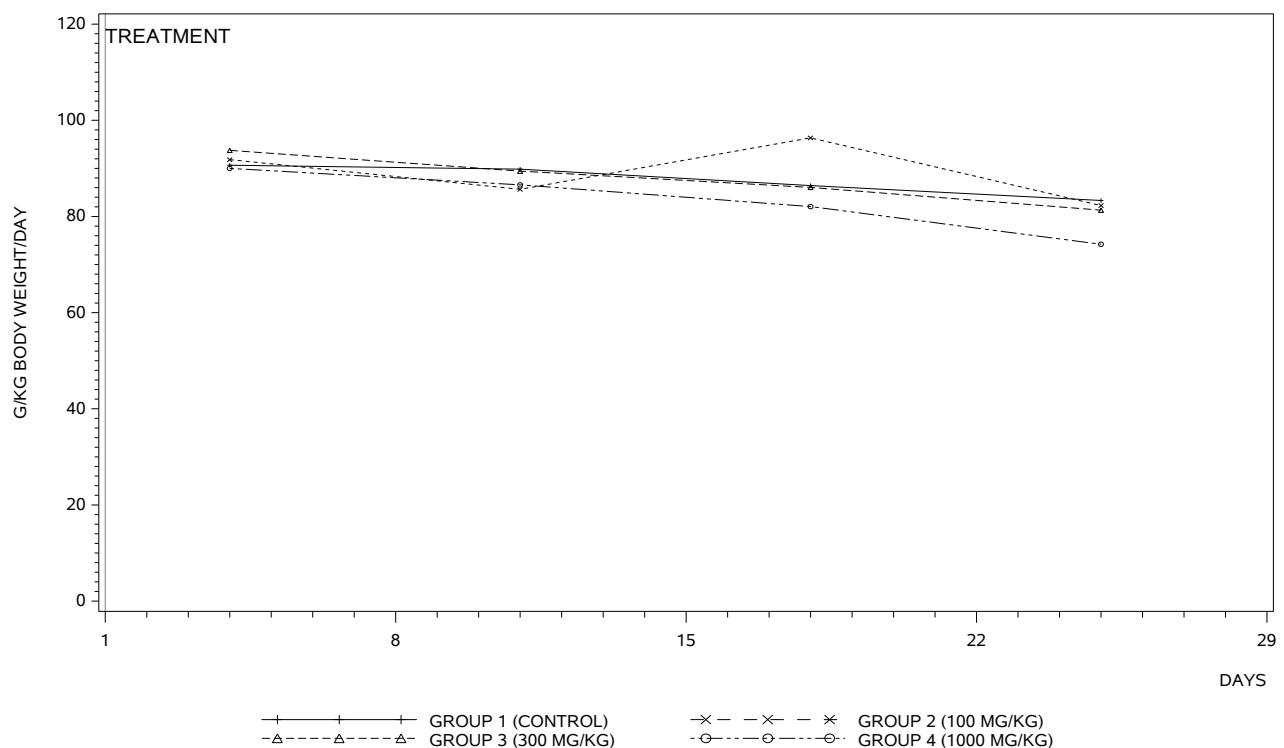
1.3 FOOD CONSUMPTION (G/ANIMAL/DAY) FEMALES



1.4 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) MALES



1.4 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) FEMALES



**1.5 CLINICAL SIGNS SUMMARY
MALES**

SIGN (MAX. GRADE) (LOCATION)	TREATMENT	
	WEEK:	DAY:
	1.....4.....	1234567123456712345671234567

GROUP 1 (CONTROL)
No clinical signs noted**GROUP 2 (100 MG/KG)**Secretion / excretion
Salivation (3)G:111.....
%:222.....**GROUP 3 (300 MG/KG)**Secretion / excretion
Salivation (3)G:11111111111111111111111111111111
%:AAAAAAA.....**GROUP 4 (1000 MG/KG)**Secretion / excretion
Salivation (3)G:11111111111111111111111111111111
%:4888888.....**FEMALES**

SIGN (MAX. GRADE) (LOCATION)	TREATMENT	
	WEEK:	DAY:
	1.....4.....	1234567123456712345671234567

GROUP 1 (CONTROL)
No clinical signs noted**GROUP 2 (100 MG/KG)**

Skin / fur

Swelling (4)

G:111111.....

(Tail apex)

%:222222.....

Scabs (3)

G:1.....

(Tail)

%:2.....

Scabs (3)

G:1.111111.....

(Tail apex)

%:2.222222.....

Wound (3)

G:1111111.....

(Tail)

%:2222222.....

Secretion / excretion

Salivation (3)

G:11111111.....

%:22222222.....

GROUP 3 (300 MG/KG)

Skin / fur

Scabs (3)

G:1.....

(Shoulder left)

%:2.....

Secretion / excretion

Salivation (3)

G:11111111111111111111111111111111.....

%:2222222.....

GROUP 4 (1000 MG/KG)

Secretion / excretion

Salivation (3)

G:11111111111111111111111111111111.....

%:488888.....

G: Median value of the highest individual daily grades

%: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%)

.: Observation performed, sign not present

**1.6 FUNCTIONAL OBSERVATIONS SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
AT WEEK 4					
HEARING SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
PUPIL L SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
PUPIL R SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
STATIC R SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
GRIP FORE GRAM	MEAN ST.DEV N	882 152 5	858 296 5	877 184 5	943 214 5
GRIP HIND GRAM	MEAN ST.DEV N	453 107 5	407 30 5	394 53 5	356 57 5

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
AT WEEK 4					
HEARING SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
PUPIL L SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
PUPIL R SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
STATIC R SCORE 0/1	MEDIAN N	0 5	0 5	0 5	0 5
GRIP FORE GRAM	MEAN ST.DEV N	547 116 5	766 226 5	700 280 5	724 130 5
GRIP HIND GRAM	MEAN ST.DEV N	334 47 5	343 48 5	296 48 5	295 46 5

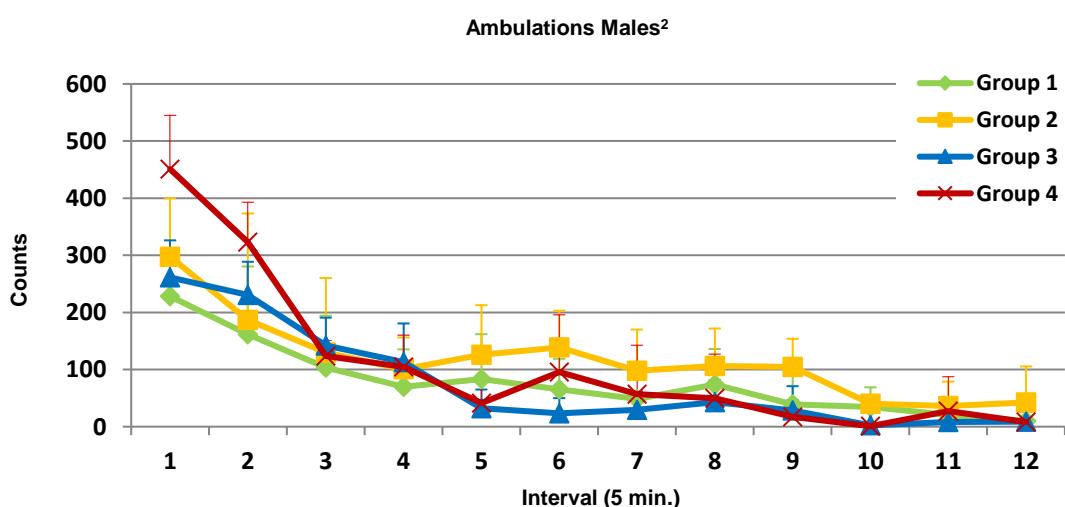
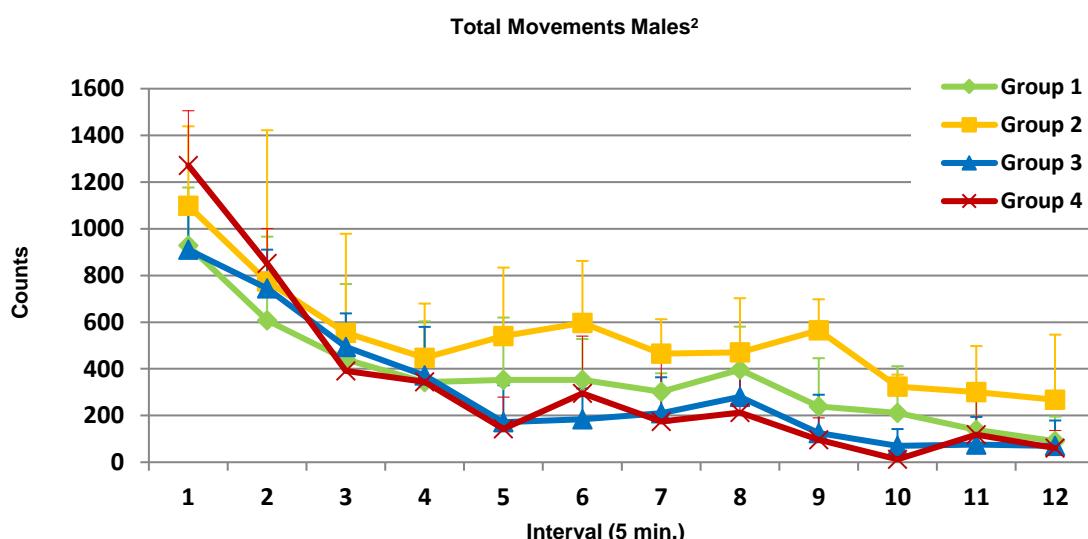
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
+/- Steel-test significant at 5% (+) or 1% (++) level

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**1.7 MOTOR ACTIVITY TEST SUMMARY
MALES**

AT WEEK 4

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
Total Movements	MEAN ¹	4405	6404	3706	3970
	ST.DEV	1533	2007	891	821
	N	5	5	5	5
Ambulations	MEAN ¹	938	1406	924	1299
	ST.DEV	484	548	204	330
	N	5	5	5	5



*/** Wilcoxon test significant at 5% (*) or 1% (**) level

¹ Group mean of all intervals combined

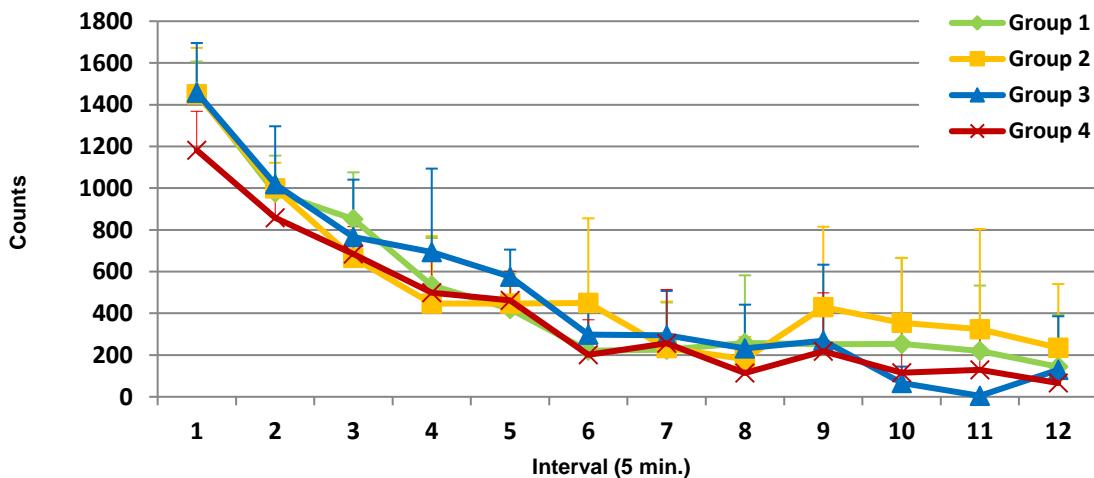
² Mean counts per interval.

**1.7 MOTOR ACTIVITY TEST SUMMARY
FEMALES**

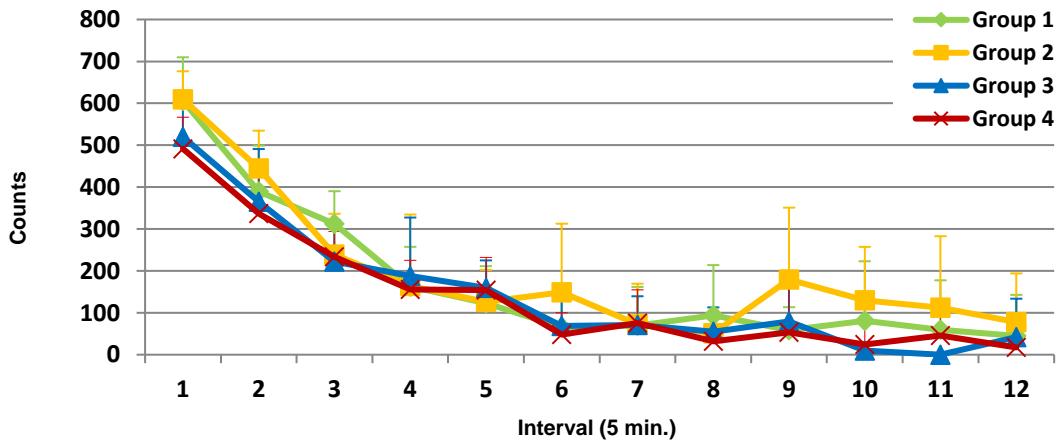
AT WEEK 4

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
Total Movements	MEAN ¹	5820	6215	5807	4785
	ST.DEV	984	1920	1445	301
	N	5	5	5	5
Ambulations	MEAN ¹	2065	2356	1780	1667
	ST.DEV	466	921	454	182
	N	5	5	5	5

Total Movements Females²



Ambulations Females²



*/** Wilcoxon test significant at 5% (*) or 1% (**) level

¹ Group mean of all intervals combined

² Mean counts per interval.

**1.8 BODY WEIGHTS (GRAM) SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAY 1	MEAN	181	175	181	180
WEEK 1	ST.DEV	4.8	8.0	7.3	8.8
	N	5	5	5	5
DAY 8	MEAN	226	214	226	217
WEEK 2	ST.DEV	9.7	12.4	6.6	14.3
	N	5	5	5	5
DAY 15	MEAN	266	244	265	249
WEEK 3	ST.DEV	12.7	17.6	8.5	18.9
	N	5	5	5	5
DAY 22	MEAN	297	268	294	269
WEEK 4	ST.DEV	17.3	23.6	8.3	21.7
	N	5	5	5	5
DAY 28	MEAN	319	285 *	311	280 *
WEEK 4	ST.DEV	19.0	25.6	10.1	20.0
	N	5	5	5	5

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAY 1	MEAN	138	136	138	137
WEEK 1	ST.DEV	6.0	6.2	5.8	6.8
	N	5	5	5	5
DAY 8	MEAN	154	153	159	160
WEEK 2	ST.DEV	6.4	6.7	5.7	9.9
	N	5	5	5	5
DAY 15	MEAN	168	170	175	179
WEEK 3	ST.DEV	5.9	5.8	8.6	11.1
	N	5	5	5	5
DAY 22	MEAN	184	179	194	192
WEEK 4	ST.DEV	7.6	11.1	7.0	13.9
	N	5	5	5	5
DAY 28	MEAN	190	188	198	203
WEEK 4	ST.DEV	9.9	11.0	7.6	13.4
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

**1.9 BODY WEIGHT GAIN (%) SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	5	5	5	5
DAY 8	MEAN	25	22	25	20 *
WEEK 2	ST.DEV	2.1	2.8	2.6	2.6
	N	5	5	5	5
DAY 15	MEAN	47	39	46	38 *
WEEK 3	ST.DEV	3.6	6.1	4.5	5.1
	N	5	5	5	5
DAY 22	MEAN	64	53	62	49 *
WEEK 4	ST.DEV	5.8	10.1	6.3	7.2
	N	5	5	5	5
DAY 28	MEAN	76	63	72	55 **
WEEK 4	ST.DEV	6.7	11.3	7.0	6.3
	N	5	5	5	5

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	5	5	5	5
DAY 8	MEAN	11	13	16	17
WEEK 2	ST.DEV	5.3	5.7	2.4	2.7
	N	5	5	5	5
DAY 15	MEAN	21	25	27 *	31 **
WEEK 3	ST.DEV	2.1	4.7	3.2	4.2
	N	5	5	5	5
DAY 22	MEAN	33	32	41	40
WEEK 4	ST.DEV	5.6	5.5	2.5	4.8
	N	5	5	5	5
DAY 28	MEAN	37	39	44	48 *
WEEK 4	ST.DEV	7.3	8.6	4.0	3.5
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

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**1.10 FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAYS 1-8	MEAN	21	20	21	18
WEEKS 1-2	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15	MEAN	23	21	24	21
WEEKS 2-3	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22	MEAN	24	21	25	21
WEEKS 3-4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-28	MEAN	24	22	24	20
WEEK 4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT	MEAN	23	21	23	20

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAYS 1-8	MEAN	14	14	15	14
WEEKS 1-2	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15	MEAN	15	15	16	16
WEEKS 2-3	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22	MEAN	16	17	17	16
WEEKS 3-4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-28	MEAN	16	16	16	15
WEEK 4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT	MEAN	15	15	16	15

**1.11 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAYS 1-8	MEAN	93	92	91	84
WEEKS 1-2	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15	MEAN	86	85	89	83
WEEKS 2-3	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22	MEAN	81	79	86	78
WEEKS 3-4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-28	MEAN	76	76	76	71
WEEK 4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT	MEAN	84	83	86	79

FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
TREATMENT					
DAYS 1-8	MEAN	91	92	94	90
WEEKS 1-2	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 8-15	MEAN	90	86	89	87
WEEKS 2-3	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 15-22	MEAN	86	96	86	82
WEEKS 3-4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
DAYS 22-28	MEAN	83	82	81	74
WEEK 4	ST.DEV	---	---	---	---
	N (CAGE)	1	1	1	1
MEAN OF MEANS OVER TREATMENT	MEAN	88	89	88	83

**1.12 HAEMATOLOGY SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
WBC 10E9/L	MEAN	9.4	8.5	9.4	10.6
	ST.DEV	2.4	0.6	1.3	2.0
	N	5	5	5	5
Neutrophils %WBC	MEAN	12.2	12.8	15.2	11.0
	ST.DEV	2.5	2.0	3.8	0.8
	N	5	5	5	5
Lymphocytes %WBC	MEAN	85.8	84.6	81.7	86.1
	ST.DEV	2.5	2.4	4.2	1.3
	N	5	5	5	5
Monocytes %WBC	MEAN	1.4	1.6	1.9	2.1
	ST.DEV	0.9	0.5	0.6	0.7
	N	5	5	5	5
Eosinophils %WBC	MEAN	0.7	0.9	1.1	0.6
	ST.DEV	0.4	0.2	0.5	0.1
	N	5	5	5	5
Basophils %WBC	MEAN	0.1	0.2	0.1	0.2
	ST.DEV	0.1	0.1	0.1	0.1
	N	5	5	5	5
Red blood cells 10E12/L	MEAN	8.77	8.72	8.97	8.95
	ST.DEV	0.43	0.13	0.32	0.27
	N	5	5	5	5
Reticulocytes %RBC	MEAN	2.9	2.7	2.3	2.3
	ST.DEV	0.2	0.3	0.4	0.4
	N	5	5	5	5
RDW %	MEAN	11.6	11.5	11.1	11.0
	ST.DEV	0.6	0.3	0.8	0.5
	N	5	5	5	5
Haemoglobin mmol/L	MEAN	9.8	10.0	10.4 *	10.2
	ST.DEV	0.2	0.4	0.2	0.3
	N	5	5	5	5
Haematocrit L/L	MEAN	0.479	0.485	0.501	0.491
	ST.DEV	0.016	0.016	0.010	0.011
	N	5	5	5	5
MCV fL	MEAN	54.7	55.6	55.9	54.8
	ST.DEV	1.1	1.7	1.4	1.1
	N	5	5	5	5
MCH fmol	MEAN	1.12	1.14	1.16	1.14
	ST.DEV	0.03	0.04	0.04	0.04
	N	5	5	5	5
MCHC mmol/L	MEAN	20.50	20.57	20.69	20.75
	ST.DEV	0.24	0.21	0.35	0.40
	N	5	5	5	5
Platelets 10E9/L	MEAN	813	736	850	874
	ST.DEV	106	41	85	81
	N	5	5	5	5

+/** Steel-test significant at 5% (+) or 1% (++) level

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

**1.12 HAEMATOLOGY SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
PT	MEAN	16.4	18.7 *	17.9	17.1
s	ST.DEV	1.3	1.6	1.1	1.3
	N	5	5	5	5
APTT	MEAN	17.4	20.7 *	20.0	18.9
s	ST.DEV	1.3	1.5	2.0	1.9
	N	4	5	5	5

+// Steel-test significant at 5% (+) or 1% (++) level

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

**1.12 HAEMATOLOGY SUMMARY
FEMALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
WBC 10E9/L	MEAN	5.3	5.0	7.1	5.9
	ST.DEV	1.1	1.6	1.9	1.7
	N	5	5	5	5
Neutrophils %WBC	MEAN	7.2	13.7 +	10.2	13.3 +
	ST.DEV	3.1	3.5	2.7	1.5
	N	5	5	5	5
Lymphocytes %WBC	MEAN	89.6	82.7 +	86.4	83.1 +
	ST.DEV	4.3	3.7	2.8	2.2
	N	5	5	5	5
Monocytes %WBC	MEAN	1.3	1.6	1.8	1.9
	ST.DEV	0.8	0.5	0.3	0.7
	N	5	5	5	5
Eosinophils %WBC	MEAN	1.7	1.9	1.5	1.6
	ST.DEV	0.8	0.5	0.3	0.6
	N	5	5	5	5
Basophils %WBC	MEAN	0.1	0.1	0.1	0.1
	ST.DEV	0.1	0.0	0.0	0.1
	N	5	5	5	5
Red blood cells 10E12/L	MEAN	8.17	8.07	8.32	8.24
	ST.DEV	0.15	0.83	0.26	0.46
	N	5	5	5	5
Reticulocytes %RBC	MEAN	2.8	2.9	2.4	2.4
	ST.DEV	0.4	1.0	0.3	0.2
	N	5	5	5	5
RDW %	MEAN	11.1	10.9	10.8	11.0
	ST.DEV	0.7	1.1	0.4	0.5
	N	5	5	5	5
Haemoglobin mmol/L	MEAN	9.3	9.1	9.3	9.1
	ST.DEV	0.1	0.9	0.3	0.5
	N	5	5	5	5
Haematocrit L/L	MEAN	0.450	0.439	0.451	0.449
	ST.DEV	0.006	0.043	0.012	0.027
	N	5	5	5	5
MCV fL	MEAN	55.1	54.4	54.2	54.4
	ST.DEV	0.6	2.1	1.2	1.2
	N	5	5	5	5
MCH fmol	MEAN	1.14	1.13	1.12	1.11
	ST.DEV	0.01	0.04	0.04	0.02
	N	5	5	5	5
MCHC mmol/L	MEAN	20.61	20.74	20.63	20.38
	ST.DEV	0.13	0.32	0.30	0.19
	N	5	5	5	5
Platelets 10E9/L	MEAN	834	844	925	804
	ST.DEV	141	64	105	305
	N	5	5	5	5

+/** Steel-test significant at 5% (+) or 1% (++) level

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

**1.12 HAEMATOLOGY SUMMARY
FEMALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
PT	MEAN	17.6	16.3	16.2	17.9
s	ST.DEV	1.6	1.0	0.2	2.4
	N	5	5	5	5
APTT	MEAN	19.3	18.3	19.1	19.1
s	ST.DEV	1.0	2.4	1.2	2.4
	N	5	5	5	5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

1.13 CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
ALAT U/L	MEAN	35.9	44.5	43.0	79.7 **
	ST.DEV	9.9	8.4	5.2	11.1
	N	5	5	5	5
ASAT U/L	MEAN	80.1	82.4	77.0	81.5
	ST.DEV	14.4	15.3	5.8	4.3
	N	5	5	5	5
ALP U/L	MEAN	195	270	197	196
	ST.DEV	36	34	66	55
	N	5	5	5	5
Total protein g/L	MEAN	64.4	65.8	68.1 **	64.8
	ST.DEV	1.8	0.9	1.9	1.7
	N	5	5	5	5
Albumin g/L	MEAN	32.7	33.9	34.9 **	34.1 *
	ST.DEV	0.5	0.7	0.8	0.8
	N	5	5	5	5
Total bilirubin umol/L	MEAN	2.0	2.1	2.0	2.2
	ST.DEV	0.3	0.3	0.2	0.5
	N	5	5	5	5
Urea mmol/L	MEAN	7.0	7.9	8.5	7.1
	ST.DEV	0.8	1.0	1.0	1.1
	N	5	5	5	5
Creatinine umol/L	MEAN	37.3	39.8	38.5	39.8
	ST.DEV	1.2	1.6	1.4	2.3
	N	5	5	5	5
Glucose mmol/L	MEAN	9.74	8.83	8.84	8.90
	ST.DEV	0.69	1.17	1.27	1.05
	N	5	5	5	5
Cholesterol mmol/L	MEAN	1.95	1.72	1.87	2.50 *
	ST.DEV	0.33	0.20	0.32	0.37
	N	5	5	5	5
Bile Acids umol/L	MEAN	25.4	74.0 *	44.2	53.3
	ST.DEV	6.6	36.9	9.9	26.7
	N	5	5	5	5
Sodium mmol/L	MEAN	139.0	142.3 **	141.4 *	139.5
	ST.DEV	0.9	2.4	0.6	0.8
	N	5	5	5	5
Potassium mmol/L	MEAN	3.80	3.62	4.00	3.77
	ST.DEV	0.12	0.21	0.29	0.17
	N	5	5	5	5
Chloride mmol/L	MEAN	101	102	102	100
	ST.DEV	1	2	1	2
	N	5	5	5	5
Calcium mmol/L	MEAN	2.58	2.58	2.62	2.65 *
	ST.DEV	0.02	0.04	0.04	0.04
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

**1.13 CLINICAL BIOCHEMISTRY SUMMARY
MALES**

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG	
END OF TREATMENT					
Inorg.Phos mmol/L	MEAN ST.DEV N	2.31 0.19 5	2.36 0.38 5	2.25 0.09 5	2.83 0.49 5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

1.13 CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
ALAT U/L	MEAN	33.8	31.2	33.8	58.8 **
	ST.DEV	10.4	6.1	4.6	12.9
	N	5	5	5	5
ASAT U/L	MEAN	79.4	86.9	86.3	78.9
	ST.DEV	5.8	23.1	7.9	5.9
	N	5	5	5	5
ALP U/L	MEAN	117	107	106	135
	ST.DEV	48	37	38	45
	N	5	5	5	5
Total protein g/L	MEAN	66.6	66.2	67.2	67.6
	ST.DEV	3.0	4.5	1.7	1.4
	N	5	5	5	5
Albumin g/L	MEAN	35.9	36.0	35.3	36.1
	ST.DEV	1.2	2.4	0.8	0.8
	N	5	5	5	5
Total bilirubin umol/L	MEAN	2.1	2.1	2.1	2.3
	ST.DEV	0.4	0.3	0.2	0.2
	N	5	5	5	5
Urea mmol/L	MEAN	9.0	7.0 *	7.2	7.5
	ST.DEV	1.4	1.0	1.0	1.4
	N	5	5	5	5
Creatinine umol/L	MEAN	44.6	40.7	43.6	43.4
	ST.DEV	5.5	2.4	2.5	3.7
	N	5	5	5	5
Glucose mmol/L	MEAN	6.65	6.12	6.48	6.79
	ST.DEV	0.70	0.57	0.68	0.82
	N	5	5	5	5
Cholesterol mmol/L	MEAN	1.35	1.64	1.55	2.05 *
	ST.DEV	0.21	0.25	0.30	0.51
	N	5	5	5	5
Bile Acids umol/L	MEAN	20.5	24.5	16.7	57.9 **
	ST.DEV	2.4	14.9	5.9	21.5
	N	5	5	5	5
Sodium mmol/L	MEAN	141.3	141.0	141.8	140.9
	ST.DEV	0.6	0.8	0.4	0.9
	N	5	5	5	5
Potassium mmol/L	MEAN	3.57	3.66	3.59	3.76
	ST.DEV	0.18	0.25	0.06	0.11
	N	5	5	5	5
Chloride mmol/L	MEAN	103	103	104	103
	ST.DEV	1	1	1	2
	N	5	5	5	5
Calcium mmol/L	MEAN	2.60	2.57	2.62	2.62
	ST.DEV	0.07	0.12	0.04	0.07
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

**1.13 CLINICAL BIOCHEMISTRY SUMMARY
FEMALES**

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT				
Inorg.Phos mmol/L	MEAN	1.82	1.76	1.93
	ST.DEV	0.13	0.15	0.28
	N	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

**1.14 MACROSCOPIC FINDINGS SUMMARY
MALES**

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT				
Animals examined	5	5	5	5
Animals without findings	5	4	4	4
Animals affected	0	1	1	1
Testes				
Reduced in size	0	0	0	1
Epididymides				
Nodule(s)	0	1	1	0
Reduced in size	0	0	0	1

FEMALES

	GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT				
Animals examined	5	5	5	5
Animals without findings	5	2	5	4
Animals affected	0	3	0	1
Liver				
Reduced in size	0	0	0	1
Uterus				
Contains fluid	0	2	0	1
Adrenal glands				
Enlarged	0	2	0	0

**1.15 ORGAN WEIGHTS (GRAM) SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W. (GRAM)	MEAN	293	262 *	285	256 *
	ST.DEV	15	24	10	22
	N	5	5	5	5
BRAIN (GRAM)	MEAN	1.95	1.87	1.97	1.90
	ST.DEV	0.09	0.07	0.08	0.08
	N	5	5	5	5
HEART (GRAM)	MEAN	0.796	0.760	0.754	0.700 *
	ST.DEV	0.049	0.069	0.036	0.057
	N	5	5	5	5
LIVER (GRAM)	MEAN	8.36	6.83 *	8.17	7.59
	ST.DEV	0.97	0.98	0.56	0.70
	N	5	5	5	5
THYROIDS (GRAM)	MEAN	0.014	0.013	0.012	0.013
	ST.DEV	0.004	0.002	0.002	0.003
	N	5	5	5	5
THYMUS (GRAM)	MEAN	0.522	0.413	0.406	0.375 *
	ST.DEV	0.113	0.080	0.078	0.063
	N	5	5	5	5
KIDNEYS (GRAM)	MEAN	2.00	1.72 *	1.89	1.74 *
	ST.DEV	0.12	0.16	0.07	0.18
	N	5	5	5	5
ADRENALS (GRAM)	MEAN	0.065	0.051 **	0.060	0.054 *
	ST.DEV	0.009	0.007	0.004	0.004
	N	5	5	5	5
SPLEEN (GRAM)	MEAN	0.531	0.465	0.478	0.404 **
	ST.DEV	0.050	0.070	0.033	0.064
	N	5	5	5	5
TESTES (GRAM)	MEAN	3.32	3.06	3.11	2.66
	ST.DEV	0.17	0.31	0.18	1.05
	N	5	5	5	5
PROSTATE GLAND (GRAM)	MEAN	0.495	0.523	0.545	0.441
	ST.DEV	0.066	0.082	0.071	0.103
	N	5	5	5	5
EPIDIDYMIDES (GRAM)	MEAN	0.859	0.792	0.774	0.671
	ST.DEV	0.099	0.062	0.085	0.193
	N	5	5	5	5
SEMINAL VESICLES (GRAM)	MEAN	0.806	0.767	0.675	0.533 *
	ST.DEV	0.168	0.161	0.133	0.076
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

**1.15 ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
MALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W. (GRAM)	MEAN	293	262 *	285	256 *
	ST.DEV	15	24	10	22
	N	5	5	5	5
BRAIN (%)	MEAN	0.67	0.72	0.69	0.74 *
	ST.DEV	0.05	0.05	0.03	0.05
	N	5	5	5	5
HEART (%)	MEAN	0.272	0.290	0.265	0.274
	ST.DEV	0.012	0.018	0.014	0.012
	N	5	5	5	5
LIVER (%)	MEAN	2.85	2.60	2.87	2.97
	ST.DEV	0.21	0.18	0.12	0.10
	N	5	5	5	5
THYROIDS (%)	MEAN	0.005	0.005	0.004	0.005
	ST.DEV	0.001	0.001	0.001	0.001
	N	5	5	5	5
THYMUS (%)	MEAN	0.177	0.157	0.143	0.146
	ST.DEV	0.031	0.025	0.027	0.013
	N	5	5	5	5
KIDNEYS (%)	MEAN	0.68	0.66	0.66	0.68
	ST.DEV	0.02	0.04	0.01	0.06
	N	5	5	5	5
ADRENALS (%)	MEAN	0.022	0.019	0.021	0.021
	ST.DEV	0.003	0.001	0.002	0.002
	N	5	5	5	5
SPLEEN (%)	MEAN	0.181	0.177	0.168	0.158
	ST.DEV	0.018	0.014	0.017	0.020
	N	5	5	5	5
TESTES (%)	MEAN	1.14	1.17	1.09	1.04
	ST.DEV	0.10	0.15	0.08	0.40
	N	5	5	5	5
PROSTATE GLAND (%)	MEAN	0.170	0.200	0.191	0.173
	ST.DEV	0.028	0.027	0.023	0.039
	N	5	5	5	5
EPIDIDYIMIDES (%)	MEAN	0.293	0.303	0.272	0.261
	ST.DEV	0.034	0.021	0.029	0.067
	N	5	5	5	5
SEMINAL VESICLES (%)	MEAN	0.275	0.297	0.237	0.208
	ST.DEV	0.056	0.081	0.048	0.021
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

**1.15 ORGAN WEIGHTS (GRAM) SUMMARY
FEMALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W. (GRAM)	MEAN	176	173	181	182
	ST.DEV	8	7	7	11
	N	5	5	5	5
BRAIN (GRAM)	MEAN	1.80	1.75	1.81	1.79
	ST.DEV	0.06	0.04	0.05	0.03
	N	5	5	5	5
HEART (GRAM)	MEAN	0.542	0.560	0.567	0.596
	ST.DEV	0.016	0.033	0.026	0.052
	N	5	5	5	5
LIVER (GRAM)	MEAN	4.65	4.73	4.91	5.76 **
	ST.DEV	0.33	0.41	0.26	0.82
	N	5	5	5	5
THYROIDS (GRAM)	MEAN	0.012	0.012	0.013	0.012
	ST.DEV	0.002	0.001	0.002	0.002
	N	5	5	5	5
THYMUS (GRAM)	MEAN	0.383	0.382	0.363	0.371
	ST.DEV	0.062	0.054	0.054	0.049
	N	5	5	5	5
KIDNEYS (GRAM)	MEAN	1.33	1.35	1.31	1.33
	ST.DEV	0.09	0.13	0.07	0.16
	N	5	5	5	5
ADRENALS (GRAM)	MEAN	0.063	0.059	0.063	0.059
	ST.DEV	0.006	0.016	0.006	0.004
	N	5	5	5	5
SPLEEN (GRAM)	MEAN	0.349	0.358	0.377	0.380
	ST.DEV	0.032	0.048	0.059	0.027
	N	5	5	5	5
OVARIES (GRAM)	MEAN	0.115	0.123	0.126	0.128
	ST.DEV	0.009	0.014	0.019	0.015
	N	5	5	5	5
UTERUS (GRAM)	MEAN	0.352	0.516	0.411	0.521
	ST.DEV	0.030	0.210	0.080	0.163
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

**1.15 ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
FEMALES**

		GROUP 1 CONTROL	GROUP 2 100 MG/KG	GROUP 3 300 MG/KG	GROUP 4 1000 MG/KG
END OF TREATMENT					
BODY W. (GRAM)	MEAN	176	173	181	182
	ST.DEV	8	7	7	11
	N	5	5	5	5
BRAIN (%)	MEAN	1.02	1.02	1.00	0.99
	ST.DEV	0.03	0.05	0.02	0.05
	N	5	5	5	5
HEART (%)	MEAN	0.309	0.325	0.313	0.328
	ST.DEV	0.013	0.017	0.008	0.025
	N	5	5	5	5
LIVER (%)	MEAN	2.65	2.74	2.71	3.16 **
	ST.DEV	0.20	0.16	0.10	0.34
	N	5	5	5	5
THYROIDS (%)	MEAN	0.007	0.007	0.007	0.007
	ST.DEV	0.001	0.001	0.001	0.001
	N	5	5	5	5
THYMUS (%)	MEAN	0.218	0.221	0.200	0.204
	ST.DEV	0.030	0.030	0.026	0.029
	N	5	5	5	5
KIDNEYS (%)	MEAN	0.76	0.78	0.72	0.73
	ST.DEV	0.07	0.05	0.01	0.08
	N	5	5	5	5
ADRENALS (%)	MEAN	0.036	0.034	0.035	0.032
	ST.DEV	0.004	0.009	0.003	0.002
	N	5	5	5	5
SPLEEN (%)	MEAN	0.199	0.208	0.208	0.209
	ST.DEV	0.016	0.028	0.027	0.015
	N	5	5	5	5
OVARIES (%)	MEAN	0.066	0.071	0.069	0.070
	ST.DEV	0.007	0.006	0.009	0.005
	N	5	5	5	5
UTERUS (%)	MEAN	0.201	0.298	0.226	0.289
	ST.DEV	0.025	0.118	0.038	0.101
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

20Dec16 12h36

APPENDIX 2
INDIVIDUAL DATA TABLES

**2.1 MORTALITY DATA
MALES**

ANIMAL	SCHEDULED SACRIFICE	TREATMENT FROM	TO
GROUP 1 (CONTROL)			
1	11NOV16	14OCT16	10NOV16
2	11NOV16	14OCT16	10NOV16
3	11NOV16	14OCT16	10NOV16
4	11NOV16	14OCT16	10NOV16
5	11NOV16	14OCT16	10NOV16
GROUP 2 (100 MG/KG)			
6	11NOV16	14OCT16	10NOV16
7	11NOV16	14OCT16	10NOV16
8	11NOV16	14OCT16	10NOV16
9	11NOV16	14OCT16	10NOV16
10	11NOV16	14OCT16	10NOV16
GROUP 3 (300 MG/KG)			
11	11NOV16	14OCT16	10NOV16
12	11NOV16	14OCT16	10NOV16
13	11NOV16	14OCT16	10NOV16
14	11NOV16	14OCT16	10NOV16
15	11NOV16	14OCT16	10NOV16
GROUP 4 (1000 MG/KG)			
16	11NOV16	14OCT16	10NOV16
17	11NOV16	14OCT16	10NOV16
18	11NOV16	14OCT16	10NOV16
19	11NOV16	14OCT16	10NOV16
20	11NOV16	14OCT16	10NOV16

FEMALES

ANIMAL	SCHEDULED SACRIFICE	TREATMENT FROM	TO
GROUP 1 (CONTROL)			
21	11NOV16	14OCT16	10NOV16
22	11NOV16	14OCT16	10NOV16
23	11NOV16	14OCT16	10NOV16
24	11NOV16	14OCT16	10NOV16
25	11NOV16	14OCT16	10NOV16
GROUP 2 (100 MG/KG)			
26	11NOV16	14OCT16	10NOV16
27	11NOV16	14OCT16	10NOV16
28	11NOV16	14OCT16	10NOV16
29	11NOV16	14OCT16	10NOV16
30	11NOV16	14OCT16	10NOV16
GROUP 3 (300 MG/KG)			
31	11NOV16	14OCT16	10NOV16
32	11NOV16	14OCT16	10NOV16
33	11NOV16	14OCT16	10NOV16
34	11NOV16	14OCT16	10NOV16
35	11NOV16	14OCT16	10NOV16
GROUP 4 (1000 MG/KG)			
36	11NOV16	14OCT16	10NOV16
37	11NOV16	14OCT16	10NOV16
38	11NOV16	14OCT16	10NOV16
39	11NOV16	14OCT16	10NOV16
40	11NOV16	14OCT16	10NOV16

**2.2 CLINICAL SIGNS
MALES**

SIGN (MAX. GRADE) (LOCATION)	TREATMENT
	WEEK: 1.....4.....
	DAY: 1234567123456712345671234567
GROUP 1 (CONTROL)	
ANIMAL 1	No clinical signs noted
ANIMAL 2	No clinical signs noted
ANIMAL 3	No clinical signs noted
ANIMAL 4	No clinical signs noted
ANIMAL 5	No clinical signs noted
GROUP 2 (100 MG/KG)	
ANIMAL 6	No clinical signs noted
ANIMAL 7	No clinical signs noted
ANIMAL 8	Secretion / excretion Salivation (3)
ANIMAL 9	G:111.....
ANIMAL 10	No clinical signs noted
ANIMAL 11	No clinical signs noted
GROUP 3 (300 MG/KG)	
ANIMAL 11	Secretion / excretion Salivation (3)
ANIMAL 12	G:1111111111111111
ANIMAL 13	Secretion / excretion Salivation (3)
ANIMAL 14	G:1111111111111111
ANIMAL 15	Secretion / excretion Salivation (3)
ANIMAL 16	G:1111111111111111
GROUP 4 (1000 MG/KG)	
ANIMAL 16	Secretion / excretion Salivation (3)
ANIMAL 17	G: ..111111111111111111111111
ANIMAL 18	Secretion / excretion Salivation (3)
ANIMAL 19	G: ..111111111111111111111111
ANIMAL 20	Secretion / excretion Salivation (3)

G: Highest daily grades
. : Observation performed, sign not present

19Jan17 09h34

**2.2 CLINICAL SIGNS
FEMALES**

SIGN (MAX. GRADE) (LOCATION)	TREATMENT
	WEEK: 1.....4..... DAY: 1234567123456712345671234567
GROUP 1 (CONTROL)	
ANIMAL 21	
No clinical signs noted	
ANIMAL 22	
No clinical signs noted	
ANIMAL 23	
No clinical signs noted	
ANIMAL 24	
No clinical signs noted	
ANIMAL 25	
No clinical signs noted	
GROUP 2 (100 MG/KG)	
ANIMAL 26	
Skin / fur	
Swelling (4) (Tail apex)	G:111111.....
Scabs (3) (Tail)	G:1.....
Scabs (3) (Tail apex)	G:1.111111.....
Wound (3) (Tail)	G:1111111.....
Secretion / excretion	
Salivation (3)	G:11111111
ANIMAL 27	
No clinical signs noted	
ANIMAL 28	
No clinical signs noted	
ANIMAL 29	
No clinical signs noted	
ANIMAL 30	
No clinical signs noted	
GROUP 3 (300 MG/KG)	
ANIMAL 31	
Secretion / excretion	
Salivation (3)	G:1111111111111111
ANIMAL 32	
Secretion / excretion	
Salivation (3)	G:1111111111111111
ANIMAL 33	
Secretion / excretion	
Salivation (3)	G:1111111111111111
ANIMAL 34	
Secretion / excretion	
Salivation (3)	G:1111111111111111
ANIMAL 35	
Skin / fur	
Scabs (3) (Shoulder left)	G:1.
Secretion / excretion	
Salivation (3)	G:1111111111111111
GROUP 4 (1000 MG/KG)	
ANIMAL 36	
Secretion / excretion	
Salivation (3)	G: ..111111111111111111111111
ANIMAL 37	
Secretion / excretion	
Salivation (3)	G: ..111111111111111111111111

G: Highest daily grades
.: Observation performed, sign not present

**2.2 CLINICAL SIGNS
FEMALES**

SIGN (MAX. GRADE) (LOCATION)	TREATMENT
	WEEK: 1.....4..... DAY: 1234567123456712345671234567

GROUP 4 (1000 MG/KG)

ANIMAL 38

Secretion / excretion
Salivation (3)

G: . 11111111111111111111111111111111

ANIMAL 39

Secretion / excretion
Salivation (3)

G: 111111111111111111111111

ANIMAL 40

Secretion / excretion
Salivation (3)

G: . 111111111111111111111111

G: Highest daily grades
. Observation performed, sign not present

19Jan17 09h34

**2.3 FUNCTIONAL OBSERVATIONS
MALES****AT WEEK 4**

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP FORE GRAM	GRIP HIND GRAM
GROUP 1 (CONTROL)						
1	0	0	0	0	877	279
2	0	0	0	0	976	434
3	0	0	0	0	625	489
4	0	0	0	0	1011	511
5	0	0	0	0	919	554
GROUP 2 (100 MG/KG)						
6	0	0	0	0	1086	387
7	0	0	0	0	543	412
8	0	0	0	0	679	369
9	0	0	0	0	735	443
10	0	0	0	0	1249	426
GROUP 3 (300 MG/KG)						
11	0	0	0	0	1015	473
12	0	0	0	0	1109	385
13	0	0	0	0	649	410
14	0	0	0	0	788	331
15	0	0	0	0	823	371
GROUP 4 (1000 MG/KG)						
16	0	0	0	0	572	260
17	0	0	0	0	1114	397
18	0	0	0	0	1049	349
19	0	0	0	0	1015	386
20	0	0	0	0	964	387

FEMALES**AT WEEK 4**

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP FORE GRAM	GRIP HIND GRAM
GROUP 1 (CONTROL)						
21	0	0	0	0	383	273
22	0	0	0	0	687	333
23	0	0	0	0	487	303
24	0	0	0	0	581	381
25	0	0	0	0	597	378
GROUP 2 (100 MG/KG)						
26	0	0	0	0	453	333
27	0	0	0	0	1077	327
28	0	0	0	0	734	277
29	0	0	0	0	844	403
30	0	0	0	0	721	375
GROUP 3 (300 MG/KG)						
31	0	0	0	0	1166	305
32	0	0	0	0	719	289
33	0	0	0	0	483	220
34	0	0	0	0	649	349
35	0	0	0	0	485	317
GROUP 4 (1000 MG/KG)						
36	0	0	0	0	839	310
37	0	0	0	0	860	354
38	0	0	0	0	540	302
39	0	0	0	0	691	228

**2.3 FUNCTIONAL OBSERVATIONS
FEMALES**

AT WEEK 4

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP FORE GRAM	GRIP HIND GRAM
GROUP 4 (1000 MG/KG)						
40	0	0	0	0	690	279

20Dec16 13h37

2.4 MOTOR ACTIVITY TEST - TOTAL MOVEMENTS
MALES

AT WEEK 4

ANIMAL	Interval (5 min.)												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
GROUP 1 (CONTROL)													
1	846	385	228	356	194	153	181	265	67	1	28	22	2726
2	1064	126	155	33	27	200	298	446	348	481	265	264	3707
3	1086	981	692	646	735	479	296	553	525	282	122	4	6401
4	526	641	251	138	430	374	395	147	23	268	281	111	3585
5	1117	908	877	544	380	559	341	569	234	26	0	50	5605
GROUP 2 (100 MG/KG)													
6	1524	1894	1240	530	649	855	433	432	555	335	598	747	9792
7	1094	424	158	592	837	602	672	724	772	334	346	33	6588
8	1311	429	654	570	563	605	261	104	550	300	69	227	5643
9	647	347	296	507	603	760	467	513	401	257	189	207	5194
10	916	778	420	34	51	164	495	582	548	395	297	123	4803
GROUP 3 (300 MG/KG)													
11	718	565	287	33	182	264	243	266	13	35	8	3	2617
12	1023	978	538	357	0	127	104	144	127	24	65	7	3494
13	840	612	492	558	311	182	290	417	74	115	283	254	4428
14	775	742	687	526	342	346	402	370	405	174	19	0	4788
15	1196	824	463	383	25	0	14	203	5	3	0	85	3201
GROUP 4 (1000 MG/KG)													
16	1234	848	456	262	117	298	111	0	62	15	17	35	3455
17	1595	1054	455	416	11	619	654	404	89	2	15	0	5314
18	1337	937	371	396	50	68	7	632	257	6	10	63	4134
19	1248	693	331	480	172	444	98	10	56	29	126	16	3703
20	943	723	341	171	361	44	0	20	20	9	424	189	3245

2.4 MOTOR ACTIVITY TEST - AMBULATIONS
MALES

AT WEEK 4

ANIMAL	Interval (5 min.)												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
GROUP 1 (CONTROL)													
1	205	75	36	60	25	1	39	32	3	0	0	1	477
2	221	15	13	0	1	37	37	49	68	78	64	47	630
3	269	278	170	145	200	97	69	142	122	51	1	0	1544
4	113	164	71	14	112	55	46	8	0	45	37	1	666
5	333	278	226	129	79	138	52	138	1	0	0	0	1374
GROUP 2 (100 MG/KG)													
6	426	476	341	148	141	209	72	116	105	21	104	151	2310
7	304	65	0	120	245	150	198	188	185	39	27	0	1521
8	337	63	139	109	125	141	4	5	88	51	0	45	1107
9	145	55	49	121	118	160	81	113	51	39	2	8	942
10	276	275	120	4	1	34	133	110	94	50	48	7	1152
GROUP 3 (300 MG/KG)													
11	217	186	95	4	28	67	31	55	0	0	0	0	683
12	249	264	133	102	0	7	0	1	25	1	0	0	782
13	271	157	123	151	67	28	41	73	15	2	41	44	1013
14	202	249	224	183	65	16	76	82	102	9	0	0	1208
15	367	298	137	124	1	0	0	4	0	0	0	1	932
GROUP 4 (1000 MG/KG)													
16	352	258	155	56	28	66	41	0	0	0	0	0	956
17	578	442	149	145	0	222	206	73	7	0	0	0	1822
18	426	296	110	131	17	9	0	176	70	0	0	0	1235
19	516	314	114	157	40	179	38	0	9	4	0	0	1371
20	382	306	91	34	120	1	0	0	1	0	135	40	1110

**2.4 MOTOR ACTIVITY TEST - TOTAL MOVEMENTS
FEMALES**

AT WEEK 4

ANIMAL	Interval (5 min.)												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
GROUP 1 (CONTROL)													
21	1595	1202	894	439	608	22	23	11	17	143	747	589	6290
22	1245	800	618	254	455	423	179	5	305	76	30	49	4439
23	1595	805	780	613	348	562	508	485	313	41	19	22	6091
24	1461	1003	756	495	147	3	411	716	205	20	31	34	5282
25	1405	1087	1212	868	544	98	6	72	420	987	272	26	6997
GROUP 2 (100 MG/KG)													
26	1617	1134	917	765	466	127	40	170	752	723	1083	521	8315
27	1471	1038	691	803	597	628	415	332	503	535	523	614	8150
28	1253	1046	702	107	218	27	1	211	834	450	2	18	4869
29	1202	805	507	378	424	428	205	37	56	42	11	12	4107
30	1710	970	513	178	527	1037	505	153	3	20	5	14	5635
GROUP 3 (300 MG/KG)													
31	1100	789	549	284	378	82	5	295	463	157	0	24	4126
32	1544	691	490	348	677	409	233	33	1	16	0	12	4454
33	1366	1224	797	634	555	158	261	526	48	3	13	589	6174
34	1729	1340	1186	1188	709	556	404	26	9	11	5	8	7171
35	1550	1054	807	1016	557	284	575	282	822	147	6	10	7110
GROUP 4 (1000 MG/KG)													
36	1185	725	641	498	537	384	228	24	146	70	21	18	4477
37	988	765	570	308	451	43	15	22	704	458	194	85	4603
38	1106	785	585	361	467	372	499	329	57	36	389	219	5205
39	1489	1176	881	742	614	47	2	10	6	8	5	7	4987
40	1141	835	749	584	242	157	542	188	175	2	39	1	4655

2.4 MOTOR ACTIVITY TEST - AMBULATIONS
FEMALES

AT WEEK 4

ANIMAL	Interval (5 min.)												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
GROUP 1 (CONTROL)													
21	680	559	352	129	240	2	0	0	0	67	270	220	2519
22	488	257	193	27	164	137	5	1	64	7	0	2	1345
23	735	350	318	223	91	179	171	198	90	1	0	1	2357
24	605	390	298	157	1	0	170	249	9	0	1	0	1880
25	522	392	402	276	118	8	0	20	130	330	25	1	2224
GROUP 2 (100 MG/KG)													
26	652	566	384	330	150	1	1	74	294	295	387	131	3265
27	694	471	282	363	213	268	164	103	229	200	172	259	3418
28	610	474	222	3	4	0	0	78	374	149	0	0	1914
29	567	342	149	97	120	111	6	1	1	5	1	0	1400
30	525	368	159	29	143	366	192	0	0	0	0	0	1782
GROUP 3 (300 MG/KG)													
31	490	300	157	25	97	2	0	67	177	7	0	2	1324
32	473	228	129	77	264	122	21	3	0	0	0	0	1317
33	496	462	234	198	129	18	68	142	1	0	0	206	1954
34	652	530	384	368	179	162	91	1	1	1	0	1	2370
35	488	306	207	270	130	39	175	62	216	42	0	0	1935
GROUP 4 (1000 MG/KG)													
36	464	271	242	189	188	111	64	0	2	0	3	1	1535
37	422	286	174	87	120	0	0	0	256	121	63	25	1554
38	445	284	204	83	150	97	137	125	1	0	160	60	1746
39	612	485	333	244	261	15	0	2	1	0	1	0	1954
40	514	358	214	176	51	18	175	32	8	1	1	0	1548

**2.5 BODY WEIGHTS (GRAM)
MALES**

TREATMENT						
ANIMAL	1	8	15	22	28	
1	175	214	254	280	303	
2	188	241	287	324	348	
3	182	226	261	287	306	
4	182	227	268	304	328	
5	179	223	260	292	309	
GROUP 1 (CONTROL)						
6	184	225	260	290	307	
7	173	215	252	283	304	
8	180	218	241	255	271	
9	163	193	215	233	247	
10	175	220	252	279	297	
GROUP 2 (100 MG/KG)						
11	187	234	276	301	320	
12	174	220	263	293	310	
13	182	229	269	303	322	
14	190	228	264	289	305	
15	174	218	253	283	298	
GROUP 3 (300 MG/KG)						
16	188	233	271	299	308	
17	169	197	221	238	252	
18	183	221	257	271	280	
19	173	208	241	265	277	
20	188	225	255	271	284	
GROUP 4 (1000 MG/KG)						

20Dec16 13h37

**2.5 BODY WEIGHTS (GRAM)
FEMALES**

TREATMENT						
ANIMAL	1	8	15	22	28	
DAYS	1	8	15	22	28	
WEEKS	1	2	3	4	4	
GROUP 1 (CONTROL)						
21	139	158	167	184	193	
22	143	163	173	196	205	
23	140	148	172	184	189	
24	128	150	158	178	184	
25	142	150	168	177	179	
GROUP 2 (100 MG/KG)						
26	138	160	177	187	195	
27	140	161	175	194	204	
28	143	147	167	178	177	
29	129	148	164	170	181	
30	130	151	166	168	185	
GROUP 3 (300 MG/KG)						
31	129	152	161	182	189	
32	138	161	174	192	202	
33	137	155	180	197	192	
34	145	164	180	199	202	
35	140	165	182	198	207	
GROUP 4 (1000 MG/KG)						
36	148	174	193	211	224	
37	134	161	183	194	203	
38	132	150	171	175	189	
39	132	151	165	183	194	
40	139	164	184	198	205	

20Dec16 13h37

**2.6 BODY WEIGHT GAIN (%)
MALES**

TREATMENT

	1	8	15	22	28
DAYS	1	2	3	4	4
WEEKS					

GROUP 1 (CONTROL)

1	0	22	45	60	73
2	0	28	53	72	85
3	0	24	43	58	68
4	0	25	47	67	80
5	0	25	45	63	73

GROUP 2 (100 MG/KG)

6	0	22	41	58	67
7	0	24	46	64	76
8	0	21	34	42	51
9	0	18	32	43	52
10	0	26	44	59	70

GROUP 3 (300 MG/KG)

11	0	25	48	61	71
12	0	26	51	68	78
13	0	26	48	66	77
14	0	20	39	52	61
15	0	25	45	63	71

GROUP 4 (1000 MG/KG)

16	0	24	44	59	64
17	0	17	31	41	49
18	0	21	40	48	53
19	0	20	39	53	60
20	0	20	36	44	51

**2.6 BODY WEIGHT GAIN (%)
FEMALES**

TREATMENT						
ANIMAL	1	8	15	22	28	
WEEKS	1	2	3	4	4	
GROUP 1 (CONTROL)						
21	0	14	20	32	39	
22	0	14	21	37	43	
23	0	6	23	31	35	
24	0	17	23	39	44	
25	0	6	18	25	26	
GROUP 2 (100 MG/KG)						
26	0	16	28	36	41	
27	0	15	25	39	46	
28	0	3	17	24	24	
29	0	15	27	32	40	
30	0	16	28	29	42	
GROUP 3 (300 MG/KG)						
31	0	18	25	41	47	
32	0	17	26	39	46	
33	0	13	31	44	40	
34	0	13	24	37	39	
35	0	18	30	41	48	
GROUP 4 (1000 MG/KG)						
36	0	18	30	43	51	
37	0	20	37	45	51	
38	0	14	30	33	43	
39	0	14	25	39	47	
40	0	18	32	42	47	

2.7 FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

TREATMENT				
DAYS	1-8	8-15	15-22	22-28
WEEKS	1-2	2-3	3-4	4
CAGE				
GROUP 1 (CONTROL)				
1	21	23	24	24
GROUP 2 (100 MG/KG)				
2	20	21	21	22
GROUP 3 (300 MG/KG)				
3	21	24	25	24
GROUP 4 (1000 MG/KG)				
4	18	21	21	20

FEMALES

TREATMENT				
DAYS	1-8	8-15	15-22	22-28
WEEKS	1-2	2-3	3-4	4
CAGE				
GROUP 1 (CONTROL)				
5	14	15	16	16
GROUP 2 (100 MG/KG)				
6	14	15	17	16
GROUP 3 (300 MG/KG)				
7	15	16	17	16
GROUP 4 (1000 MG/KG)				
8	14	16	16	15

**2.8 RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY)
MALES**

TREATMENT				
DAY	1-8	8-15	15-22	22-28
WEEKS	1-2	2-3	3-4	4
CAGE				
GROUP 1 (CONTROL)				
1	93	86	81	76
GROUP 2 (100 MG/KG)				
2	92	85	79	76
GROUP 3 (300 MG/KG)				
3	91	89	86	76
GROUP 4 (1000 MG/KG)				
4	84	83	78	71

FEMALES

TREATMENT				
DAY	1-8	8-15	15-22	22-28
WEEKS	1-2	2-3	3-4	4
CAGE				
GROUP 1 (CONTROL)				
5	91	90	86	83
GROUP 2 (100 MG/KG)				
6	92	86	96	82
GROUP 3 (300 MG/KG)				
7	94	89	86	81
GROUP 4 (1000 MG/KG)				
8	90	87	82	74

2.9 HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	WBC 10E9/L	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
1	10.2	8.0	89.1	2.1	0.7
2	12.0	13.0	86.0	1.0	0.0
3	9.0	14.1	83.0	2.0	0.9
4	10.1	12.0	87.0	0.0	1.0
5	5.5	13.7	83.7	1.7	0.9
GROUP 2 (100 MG/KG)					
6	7.9	10.2	87.8	1.1	0.8
7	9.4	15.2	81.4	2.1	1.1
8	8.7	13.9	83.5	2.1	0.5
9	8.5	11.4	85.9	1.4	1.1
10	8.2	13.2	84.4	1.4	0.9
GROUP 3 (300 MG/KG)					
11	8.0	17.5	79.9	1.7	0.7
12	11.0	11.3	84.7	2.3	1.6
13	8.1	14.6	83.6	1.2	0.5
14	10.4	12.3	85.0	1.5	0.9
15	9.4	20.5	75.2	2.7	1.6
GROUP 4 (1000 MG/KG)					
16	9.5	11.7	84.9	2.8	0.6
17	9.4	10.0	87.9	1.3	0.7
18	11.5	11.6	84.9	2.9	0.4
19	13.6	10.2	86.9	1.7	0.8
20	8.9	11.6	85.9	1.8	0.6

MALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/L	Reticulocytes %RBC	RDW %	Haemoglobin mmol/L
GROUP 1 (CONTROL)					
1	0.2	8.58	3.1	12.3	9.6
2	0.0	9.28	2.6	12.1	10.0
3	0.1	9.04	2.9	11.0	10.0
4	0.0	8.79	2.8	11.1	10.0
5	0.1	8.15	3.0	11.4	9.5
GROUP 2 (100 MG/KG)					
6	0.1	8.84	2.6	11.0	10.5
7	0.2	8.74	3.0	11.8	9.9
8	0.1	8.51	2.2	11.7	10.0
9	0.3	8.70	2.5	11.6	9.9
10	0.1	8.81	3.0	11.6	9.5
GROUP 3 (300 MG/KG)					
11	0.1	8.74	1.8	10.3	10.4
12	0.2	9.28	2.1	11.1	10.7
13	0.1	8.75	2.8	10.3	10.4
14	0.2	8.73	2.5	12.0	10.1
15	0.1	9.36	2.3	11.8	10.2
GROUP 4 (1000 MG/KG)					
16	0.1	9.31	1.8	10.7	10.3
17	0.2	8.62	2.2	10.7	10.1
18	0.3	8.91	2.2	10.5	10.6
19	0.3	8.80	2.8	11.8	9.8

2.9 HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/L	Reticulocytes %RBC	RDW %	Haemoglobin mmol/L
GROUP 4 (1000 MG/KG)					
20	0.1	9.12	2.4	11.2	10.1

MALES
END OF TREATMENT

ANIMAL	Haematocrit L/L	MCV fL	MCH fmol	MCHC mmol/L	Platelets 10E9/L
GROUP 1 (CONTROL)					
1	0.468	54.5	1.12	20.49	723
2	0.494	53.2	1.08	20.23	732
3	0.491	54.4	1.10	20.32	876
4	0.486	55.3	1.14	20.64	767
5	0.457	56.0	1.17	20.83	968
GROUP 2 (100 MG/KG)					
6	0.513	58.0	1.19	20.52	746
7	0.479	54.9	1.14	20.70	726
8	0.479	56.3	1.17	20.79	682
9	0.482	55.5	1.14	20.62	728
10	0.472	53.5	1.08	20.24	796
GROUP 3 (300 MG/KG)					
11	0.500	57.3	1.19	20.78	903
12	0.509	54.8	1.15	20.96	766
13	0.503	57.5	1.19	20.63	971
14	0.484	55.5	1.16	20.95	803
15	0.509	54.4	1.09	20.12	807
GROUP 4 (1000 MG/KG)					
16	0.504	54.1	1.10	20.37	977
17	0.486	56.3	1.17	20.84	908
18	0.497	55.8	1.19	21.40	797
19	0.476	54.1	1.11	20.57	786
20	0.491	53.8	1.11	20.56	903

MALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
1	16.2	--
2	15.3	18.5
3	16.3	18.6
4	18.5	16.2
5	15.5	16.3
GROUP 2 (100 MG/KG)		
6	18.5	19.2
7	20.2	19.8
8	16.6	20.7
9	17.9	20.4
10	20.4	23.2

2.9 HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 3 (300 MG/KG)		
11	19.0	18.6
12	17.2	17.4
13	17.0	20.0
14	17.2	22.0
15	19.2	21.8
GROUP 4 (1000 MG/KG)		
16	17.5	19.6
17	19.1	20.6
18	16.5	20.6
19	16.8	16.5
20	15.7	17.2

FEMALES
END OF TREATMENT

ANIMAL	WBC 10E9/L	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
21	4.6	9.1	86.2	1.8	3.0
22	5.3	6.7	89.7	1.6	1.8
23	7.2	8.9	87.1	2.1	1.8
24	5.0	2.0	97.0	0.0	1.0
25	4.6	9.5	88.2	1.1	1.0
GROUP 2 (100 MG/KG)					
26	7.7	17.0	80.0	1.0	2.0
27	4.7	11.1	85.4	1.3	2.0
28	4.2	10.5	85.3	2.4	1.8
29	5.1	11.8	85.3	1.5	1.3
30	3.4	17.9	77.5	1.8	2.6
GROUP 3 (300 MG/KG)					
31	6.1	9.4	87.7	1.6	1.2
32	9.9	8.6	87.7	2.0	1.6
33	5.9	12.0	84.6	1.7	1.4
34	8.1	7.0	89.4	1.5	1.9
35	5.5	13.8	82.4	2.1	1.5
GROUP 4 (1000 MG/KG)					
36	3.6	12.0	86.0	1.0	1.0
37	7.8	14.9	82.5	1.4	1.2
38	4.9	11.7	84.3	2.1	1.7
39	6.2	14.8	80.1	2.5	2.5
40	7.0	13.0	82.8	2.4	1.7

FEMALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/L	Reticulocytes %RBC	RDW %	Haemoglobin mmol/L
GROUP 1 (CONTROL)					
21	0.1	8.39	2.6	11.3	9.4
22	0.1	8.26	2.4	11.0	9.4

2.9 HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/L	Reticulocytes %RBC	RDW %	Haemoglobin mmol/L
GROUP 1 (CONTROL)					
23	0.2	8.02	2.9	10.0	9.1
24	0.0	8.07	2.8	11.1	9.2
25	0.2	8.09	3.5	11.9	9.2
GROUP 2 (100 MG/KG)					
26	0.0	8.68	3.1	10.1	9.7
27	0.1	8.23	2.1	10.5	9.2
28	0.1	8.58	2.5	11.4	9.1
29	0.1	8.24	2.4	9.8	9.7
30	0.1	6.64	4.5	12.5	7.6
GROUP 3 (300 MG/KG)					
31	0.1	8.33	1.9	10.6	9.7
32	0.2	8.09	2.3	11.4	9.2
33	0.1	8.20	2.8	10.5	9.3
34	0.1	8.77	2.5	11.2	9.5
35	0.1	8.22	2.5	10.5	8.8
GROUP 4 (1000 MG/KG)					
36	0.0	7.83	2.3	11.1	8.5
37	0.1	8.71	2.6	10.5	9.7
38	0.1	7.91	2.2	10.6	8.9
39	0.0	7.99	2.7	11.8	9.0
40	0.1	8.78	2.2	11.1	9.6

FEMALES
END OF TREATMENT

ANIMAL	Haematocrit L/L	MCV fL	MCH fmol	MCHC mmol/L	Platelets 10E9/L
GROUP 1 (CONTROL)					
21	0.457	54.5	1.13	20.64	881
22	0.453	54.8	1.13	20.68	966
23	0.440	54.9	1.14	20.76	749
24	0.449	55.6	1.14	20.49	632
25	0.451	55.8	1.14	20.46	944
GROUP 2 (100 MG/KG)					
26	0.477	55.0	1.12	20.42	868
27	0.452	54.9	1.12	20.38	910
28	0.435	50.7	1.07	21.03	841
29	0.462	56.0	1.18	21.05	862
30	0.367	55.2	1.15	20.84	738
GROUP 3 (300 MG/KG)					
31	0.459	55.2	1.16	21.08	892
32	0.444	54.8	1.14	20.74	929
33	0.453	55.3	1.14	20.58	882
34	0.464	53.0	1.08	20.43	1100
35	0.435	52.9	1.07	20.32	821
GROUP 4 (1000 MG/KG)					
36	0.412	52.6	1.09	20.67	287
37	0.478	54.9	1.12	20.33	1078
38	0.439	55.5	1.13	20.28	921
39	0.441	55.2	1.13	20.45	806
40	0.474	54.0	1.09	20.17	928

2.9 HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
21	16.1	19.8
22	15.6	18.7
23	18.5	18.0
24	18.8	20.7
25	19.0	19.1
GROUP 2 (100 MG/KG)		
26	15.9	19.4
27	14.7	17.8
28	17.2	16.0
29	16.6	21.9
30	17.0	16.6
GROUP 3 (300 MG/KG)		
31	16.2	18.6
32	16.5	18.4
33	16.1	20.2
34	16.2	20.5
35	16.1	17.6
GROUP 4 (1000 MG/KG)		
36	19.0	15.1
37	15.5	18.8
38	16.7	20.4
39	16.8	20.6
40	21.6	20.7

2.10 CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	ALAT U/L	ASAT U/L	ALP U/L	Total protein g/L	Albumin g/L
GROUP 1 (CONTROL)					
1	25.9	70.5	227	61.7	32.0
2	31.7	79.6	151	63.5	32.4
3	50.2	103.6	185	65.9	33.3
4	29.8	66.7	174	65.4	32.8
5	41.8	79.9	236	65.4	32.9
GROUP 2 (100 MG/KG)					
6	36.9	88.6	256	66.9	33.8
7	40.3	71.3	289	64.9	32.7
8	38.5	101.6	233	64.8	34.2
9	55.8	87.4	319	65.9	34.2
10	51.2	63.0	252	66.3	34.4
GROUP 3 (300 MG/KG)					
11	44.5	84.8	280	69.8	36.0
12	42.2	76.7	128	67.7	33.8
13	37.5	71.6	191	70.3	35.4
14	51.1	80.7	246	65.7	34.6
15	39.9	71.4	141	67.2	34.6
GROUP 4 (1000 MG/KG)					
16	98.1	82.7	143	66.3	34.4
17	71.3	76.2	169	61.8	32.9
18	78.0	79.9	283	65.7	33.8
19	70.9	80.5	171	65.1	35.2
20	80.2	88.0	212	65.0	34.3
MALES END OF TREATMENT					
ANIMAL	Total bilirubin umol/L	Urea mmol/L	Creatinine umol/L	Glucose mmol/L	Cholesterol mmol/L
GROUP 1 (CONTROL)					
1	1.7	6.0	37.1	9.03	1.74
2	1.9	6.3	39.0	10.71	2.08
3	2.0	7.6	35.8	10.07	1.73
4	1.8	7.9	37.1	9.75	1.72
5	2.5	7.2	37.7	9.15	2.47
GROUP 2 (100 MG/KG)					
6	2.1	7.0	39.0	8.72	1.94
7	1.7	7.8	39.0	9.19	1.87
8	2.5	7.4	40.3	7.65	1.45
9	2.4	7.6	38.4	7.96	1.63
10	2.0	9.5	42.3	10.61	1.70
GROUP 3 (300 MG/KG)					
11	2.2	9.0	37.7	7.90	1.99
12	1.8	8.9	37.1	8.01	2.06
13	2.0	6.7	39.7	8.01	2.22
14	2.2	9.2	37.7	9.52	1.65
15	1.9	8.8	40.3	10.76	1.45
GROUP 4 (1000 MG/KG)					
16	1.7	7.5	39.0	7.64	1.94
17	1.8	6.2	38.4	9.93	2.72
18	2.3	6.3	37.7	8.80	2.90
19	2.9	8.9	43.6	9.98	2.39

2.10 CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/L	Urea mmol/L	Creatinine umol/L	Glucose mmol/L	Cholesterol mmol/L
GROUP 4 (1000 MG/KG)					
20	2.5	6.5	40.3	8.14	2.54

MALES
END OF TREATMENT

ANIMAL	Bile Acids umol/L	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Calcium mmol/L
GROUP 1 (CONTROL)					
1	16.9	139.5	3.90	102	2.57
2	20.5	140.2	3.79	101	2.56
3	27.1	139.2	3.70	101	2.60
4	33.4	138.0	3.66	99	2.60
5	28.9	138.3	3.95	101	2.58
GROUP 2 (100 MG/KG)					
6	68.3	143.3	3.44	101	2.61
7	138.8	140.9	3.74	100	2.52
8	51.9	146.2	3.44	105	2.56
9	60.4	140.9	3.55	102	2.61
10	50.7	140.4	3.91	102	2.61
GROUP 3 (300 MG/KG)					
11	35.0	140.8	3.80	100	2.62
12	39.0	140.8	4.37	102	2.65
13	37.3	141.9	3.66	102	2.64
14	55.1	142.0	4.20	103	2.61
15	54.7	141.3	3.96	102	2.56
GROUP 4 (1000 MG/KG)					
16	54.5	138.9	3.96	98	2.71
17	20.9	138.8	3.78	102	2.59
18	61.4	140.5	3.63	99	2.63
19	91.9	139.1	3.58	101	2.67
20	37.6	140.4	3.92	101	2.65

MALES
END OF TREATMENT

ANIMAL	Inorg.Phos mmol/L
GROUP 1 (CONTROL)	
1	2.40
2	2.10
3	2.10
4	2.42
5	2.51
GROUP 2 (100 MG/KG)	
6	2.40
7	2.36
8	2.91
9	2.28
10	1.85

2.10 CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Inorg.Phos mmol/L
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GROUP 3 (300 MG/KG)

11	2.39
12	2.21
13	2.14
14	2.27
15	2.25

GROUP 4 (1000 MG/KG)

16	2.48
17	2.30
18	2.86
19	2.94
20	3.57

FEMALES
END OF TREATMENT

ANIMAL	ALAT U/L	ASAT U/L	ALP U/L	Total protein g/L	Albumin g/L
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GROUP 1 (CONTROL)

21	25.5	82.0	112	65.8	35.5
22	45.1	70.1	175	71.8	37.8
23	29.9	79.7	149	65.0	34.7
24	23.7	79.6	100	64.5	35.3
25	44.6	85.8	49	65.8	36.3

GROUP 2 (100 MG/KG)

26	40.0	77.3	122	67.6	36.6
27	28.8	79.4	78	70.2	37.6
28	25.2	93.8	88	62.6	33.9
29	35.1	61.4	82	70.1	38.8
30	27.1	122.8	166	60.4	33.1

GROUP 3 (300 MG/KG)

31	34.6	83.7	87	69.1	36.3
32	38.0	77.8	139	67.9	34.9
33	37.8	97.8	83	64.7	34.4
34	31.4	90.4	68	67.8	35.9
35	27.1	81.9	154	66.5	35.2

GROUP 4 (1000 MG/KG)

36	57.9	80.6	108	70.1	37.3
37	80.2	74.2	191	67.2	35.4
38	56.0	85.6	92	66.4	36.2
39	54.4	71.5	108	67.1	36.3
40	45.5	82.5	177	67.4	35.5

FEMALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/L	Urea mmol/L	Creatinine umol/L	Glucose mmol/L	Cholesterol mmol/L
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GROUP 1 (CONTROL)

21	2.0	10.5	52.7	6.09	1.36
22	2.3	10.2	46.8	6.82	1.71

2.10 CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/L	Urea mmol/L	Creatinine umol/L	Glucose mmol/L	Cholesterol mmol/L
GROUP 1 (CONTROL)					
23	2.5	8.9	41.6	6.29	1.27
24	2.1	7.3	43.6	6.25	1.20
25	1.5	7.9	38.4	7.80	1.19
GROUP 2 (100 MG/KG)					
26	2.2	7.6	42.9	6.42	1.87
27	1.9	6.8	39.0	6.48	1.77
28	2.1	5.7	39.7	5.50	1.52
29	1.7	8.2	38.4	6.69	1.77
30	2.5	6.5	43.6	5.53	1.25
GROUP 3 (300 MG/KG)					
31	1.9	6.3	41.6	5.86	1.59
32	2.1	8.8	42.9	6.36	1.44
33	1.9	7.1	44.2	5.88	1.96
34	2.4	6.6	41.6	6.84	1.64
35	2.0	7.4	47.5	7.46	1.14
GROUP 4 (1000 MG/KG)					
36	2.5	8.9	47.5	6.55	1.94
37	2.2	9.1	37.7	8.02	2.94
38	2.4	6.4	43.6	6.09	1.88
39	1.9	6.2	42.9	7.19	1.78
40	2.4	7.1	45.5	6.10	1.71

FEMALES
END OF TREATMENT

ANIMAL	Bile Acids umol/L	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Calcium mmol/L
GROUP 1 (CONTROL)					
21	21.6	140.7	3.43	103	2.57
22	19.7	140.8	3.85	103	2.71
23	23.9	141.2	3.59	103	2.64
24	19.7	141.8	3.60	104	2.54
25	17.5	142.2	3.39	104	2.56
GROUP 2 (100 MG/KG)					
26	24.9	141.5	3.81	104	2.58
27	16.2	141.3	3.77	103	2.69
28	16.2	139.8	3.34	104	2.48
29	50.2	140.6	3.94	102	2.70
30	15.0	141.7	3.46	103	2.42
GROUP 3 (300 MG/KG)					
31	17.9	142.2	3.54	104	2.60
32	24.6	142.1	3.69	105	2.67
33	15.1	141.3	3.55	103	2.57
34	17.8	141.6	3.56	103	2.64
35	8.3	141.7	3.60	106	2.60
GROUP 4 (1000 MG/KG)					
36	74.9	140.4	3.90	102	2.73
37	79.7	140.1	3.59	100	2.63
38	56.2	140.2	3.75	104	2.61
39	53.6	141.9	3.76	105	2.54
40	25.3	142.0	3.80	105	2.57

2.10 CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	Inorg.Phos
	mmol/L

GROUP 1 (CONTROL)

21	1.93
22	1.81
23	1.97
24	1.71
25	1.68

GROUP 2 (100 MG/KG)

26	1.84
27	1.90
28	1.58
29	1.62
30	1.84

GROUP 3 (300 MG/KG)

31	2.10
32	1.96
33	2.09
34	1.87
35	1.65

GROUP 4 (1000 MG/KG)

36	2.33
37	1.78
38	1.75
39	1.68
40	2.11

**2.11 MACROSCOPIC FINDINGS
MALES****ALL NECROPSIES**

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
1		No findings noted	Scheduled sacrifice, 11Nov2016
2		No findings noted	Scheduled sacrifice, 11Nov2016
3		No findings noted	Scheduled sacrifice, 11Nov2016
4		No findings noted	Scheduled sacrifice, 11Nov2016
5		No findings noted	Scheduled sacrifice, 11Nov2016
GROUP 2 (100 MG/KG)			
6		No findings noted	Scheduled sacrifice, 11Nov2016
7		No findings noted	Scheduled sacrifice, 11Nov2016
8		No findings noted	Scheduled sacrifice, 11Nov2016
9		No findings noted	Scheduled sacrifice, 11Nov2016
10	Epididymides	Tail, right side: nodule(s), d=8x4 mm, yellowish, hard.	Scheduled sacrifice, 11Nov2016
GROUP 3 (300 MG/KG)			
11		No findings noted	Scheduled sacrifice, 11Nov2016
12		No findings noted	Scheduled sacrifice, 11Nov2016
13	Epididymides	Tail, left side: nodule(s), d=7x8 mm, yellowish, soft.	Scheduled sacrifice, 11Nov2016
14		No findings noted	Scheduled sacrifice, 11Nov2016
15		No findings noted	Scheduled sacrifice, 11Nov2016
GROUP 4 (1000 MG/KG)			
16		No findings noted	Scheduled sacrifice, 11Nov2016
17		No findings noted	Scheduled sacrifice, 11Nov2016
18		No findings noted	Scheduled sacrifice, 11Nov2016
19	Testes	Both sides: reduced in size.	Scheduled sacrifice, 11Nov2016
	Epididymides	Both sides: reduced in size.	Scheduled sacrifice, 11Nov2016
20		No findings noted	Scheduled sacrifice, 11Nov2016

FEMALES**ALL NECROPSIES**

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
21		No findings noted	Scheduled sacrifice, 11Nov2016
22		No findings noted	Scheduled sacrifice, 11Nov2016
23		No findings noted	Scheduled sacrifice, 11Nov2016
24		No findings noted	Scheduled sacrifice, 11Nov2016
25		No findings noted	Scheduled sacrifice, 11Nov2016
GROUP 2 (100 MG/KG)			
26	Uterus	Contains fluid.	Scheduled sacrifice, 11Nov2016
27		No findings noted	Scheduled sacrifice, 11Nov2016
28	Adrenal glands	Both sides: enlarged.	Scheduled sacrifice, 11Nov2016
29		No findings noted	Scheduled sacrifice, 11Nov2016
30	Uterus	Contains fluid.	Scheduled sacrifice, 11Nov2016
	Adrenal glands	Both sides: enlarged.	Scheduled sacrifice, 11Nov2016
GROUP 3 (300 MG/KG)			
31		No findings noted	Scheduled sacrifice, 11Nov2016
32		No findings noted	Scheduled sacrifice, 11Nov2016
33		No findings noted	Scheduled sacrifice, 11Nov2016
34		No findings noted	Scheduled sacrifice, 11Nov2016
35		No findings noted	Scheduled sacrifice, 11Nov2016
GROUP 4 (1000 MG/KG)			
36		No findings noted	Scheduled sacrifice, 11Nov2016
37		No findings noted	Scheduled sacrifice, 11Nov2016

**2.11 MACROSCOPIC FINDINGS
FEMALES**

ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 4 (1000 MG/KG)			
38	Liver	Papillary process, left side: reduced in size.	Scheduled sacrifice, 11Nov2016
	Uterus	Contains fluid.	
39		No findings noted	Scheduled sacrifice, 11Nov2016
40		No findings noted	Scheduled sacrifice, 11Nov2016

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2.12 ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)
GROUP 1 (CONTROL)				
1	278	1.83	0.760	7.54
2	315	1.92	0.850	9.95
3	284	2.02	0.815	8.49
4	300	1.93	0.825	8.18
5	288	2.06	0.730	7.64
GROUP 2 (100 MG/KG)				
6	276	1.98	0.845	6.87
7	284	1.89	0.795	7.66
8	245	1.84	0.760	5.95
9	229	1.78	0.660	5.73
10	278	1.87	0.740	7.93
GROUP 3 (300 MG/KG)				
11	294	2.07	0.720	8.76
12	285	1.86	0.795	8.57
13	292	2.02	0.790	8.33
14	283	1.94	0.725	7.79
15	269	1.96	0.740	7.40
GROUP 4 (1000 MG/KG)				
16	287	2.04	0.780	8.35
17	227	1.88	0.640	6.55
18	256	1.86	0.735	8.03
19	250	1.82	0.685	7.32
20	259	1.89	0.660	7.73

MALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 1 (CONTROL)				
1	0.010	0.505	1.93	0.070
2	0.017	0.720	2.17	0.070
3	0.014	0.475	2.02	0.070
4	0.017	0.440	2.03	0.065
5	0.010	0.470	1.85	0.050
GROUP 2 (100 MG/KG)				
6	0.014	0.540	1.91	0.055
7	0.013	0.425	1.67	0.055
8	0.014	0.325	1.70	0.050
9	0.011	0.380	1.50	0.040
10	0.010	0.395	1.84	0.055
GROUP 3 (300 MG/KG)				
11	0.013	0.305	1.94	0.055
12	0.012	0.485	1.93	0.060
13	0.009	0.485	1.95	0.060
14	0.015	0.380	1.84	0.065
15	0.011	0.375	1.80	0.060
GROUP 4 (1000 MG/KG)				
16	0.017	0.460	1.86	0.050
17	0.008	0.290	1.61	0.050
18	0.014	0.400	1.97	0.060
19	0.011	0.345	1.55	0.055

2.12 ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 4 (1000 MG/KG)				
20	0.013	0.380	1.71	0.055

MALES
END OF TREATMENT

ANIMAL	SPLEEN (GRAM)	TESTES (GRAM)	PROSTATE GLAND (GRAM)	EPIDIDYMIDES (GRAM)
GROUP 1 (CONTROL)				
1	0.550	3.40	0.500	0.835
2	0.510	3.10	0.405	0.865
3	0.490	3.42	0.490	0.935
4	0.610	3.51	0.490	0.955
5	0.495	3.19	0.590	0.705
GROUP 2 (100 MG/KG)				
6	0.480	3.46	0.485	0.845
7	0.570	3.10	0.635	0.760
8	0.405	3.21	0.415	0.795
9	0.395	2.87	0.525	0.705
10	0.475	2.65	0.555	0.855
GROUP 3 (300 MG/KG)				
11	0.450	3.11	0.615	0.730
12	0.480	3.15	0.465	0.675
13	0.440	2.85	0.515	0.875
14	0.520	3.35	0.625	0.850
15	0.500	3.09	0.505	0.740
GROUP 4 (1000 MG/KG)				
16	0.430	3.40	0.535	0.885
17	0.295	2.96	0.470	0.660
18	0.440	3.26	0.485	0.805
19	0.455	0.83	0.265	0.385
20	0.400	2.87	0.450	0.620

MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (GRAM)
GROUP 1 (CONTROL)	
1	0.980
2	0.990
3	0.685
4	0.740
5	0.635
GROUP 2 (100 MG/KG)	
6	0.760
7	0.610
8	1.035
9	0.745
10	0.685

2.12 ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (GRAM)
--------	----------------------------

GROUP 3 (300 MG/KG)

11	0.640
12	0.545
13	0.660
14	0.900
15	0.630

GROUP 4 (1000 MG/KG)

16	0.625
17	0.455
18	0.555
19	0.575
20	0.455

20Dec16 13h37

2.12 ORGAN/BODY WEIGHT RATIOS (%)**MALES****END OF TREATMENT**

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)
GROUP 1 (CONTROL)				
1	278	0.66	0.273	2.71
2	315	0.61	0.270	3.16
3	284	0.71	0.287	2.99
4	300	0.64	0.275	2.73
5	288	0.71	0.253	2.65
GROUP 2 (100 MG/KG)				
6	276	0.71	0.306	2.49
7	284	0.67	0.280	2.70
8	245	0.75	0.311	2.43
9	229	0.78	0.289	2.51
10	278	0.67	0.267	2.86
GROUP 3 (300 MG/KG)				
11	294	0.70	0.245	2.97
12	285	0.65	0.279	3.01
13	292	0.69	0.270	2.85
14	283	0.69	0.256	2.75
15	269	0.73	0.275	2.75
GROUP 4 (1000 MG/KG)				
16	287	0.71	0.272	2.91
17	227	0.83	0.282	2.89
18	256	0.72	0.287	3.13
19	250	0.73	0.274	2.92
20	259	0.73	0.255	2.98
MALES				
END OF TREATMENT				
ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 1 (CONTROL)				
1	0.004	0.182	0.69	0.025
2	0.005	0.228	0.69	0.022
3	0.005	0.167	0.71	0.025
4	0.006	0.147	0.68	0.022
5	0.003	0.163	0.64	0.017
GROUP 2 (100 MG/KG)				
6	0.005	0.195	0.69	0.020
7	0.005	0.150	0.59	0.019
8	0.006	0.133	0.69	0.020
9	0.005	0.166	0.66	0.017
10	0.004	0.142	0.66	0.020
GROUP 3 (300 MG/KG)				
11	0.004	0.104	0.66	0.019
12	0.004	0.170	0.68	0.021
13	0.003	0.166	0.67	0.021
14	0.005	0.134	0.65	0.023
15	0.004	0.139	0.67	0.022
GROUP 4 (1000 MG/KG)				
16	0.006	0.160	0.65	0.017
17	0.004	0.128	0.71	0.022
18	0.006	0.156	0.77	0.023
19	0.004	0.138	0.62	0.022

2.12 ORGAN/BODY WEIGHT RATIOS (%)**MALES****END OF TREATMENT**

ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 4 (1000 MG/KG)				
20	0.005	0.147	0.66	0.021

MALES
END OF TREATMENT

ANIMAL	SPLEEN (%)	TESTES (%)	PROSTATE GLAND (%)	EPIDIDYMIDES (%)
GROUP 1 (CONTROL)				
1	0.198	1.22	0.180	0.300
2	0.162	0.98	0.128	0.274
3	0.172	1.20	0.172	0.329
4	0.204	1.17	0.164	0.319
5	0.172	1.11	0.205	0.245
GROUP 2 (100 MG/KG)				
6	0.174	1.25	0.176	0.306
7	0.201	1.09	0.224	0.268
8	0.166	1.31	0.170	0.325
9	0.173	1.26	0.230	0.308
10	0.171	0.95	0.200	0.308
GROUP 3 (300 MG/KG)				
11	0.153	1.06	0.209	0.248
12	0.169	1.11	0.163	0.237
13	0.151	0.98	0.176	0.299
14	0.184	1.18	0.221	0.300
15	0.186	1.15	0.188	0.275
GROUP 4 (1000 MG/KG)				
16	0.150	1.18	0.186	0.308
17	0.130	1.30	0.207	0.291
18	0.172	1.27	0.189	0.314
19	0.182	0.33	0.106	0.154
20	0.154	1.11	0.174	0.239

MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (%)
GROUP 1 (CONTROL)	
1	0.353
2	0.314
3	0.241
4	0.247
5	0.220
GROUP 2 (100 MG/KG)	
6	0.275
7	0.215
8	0.423
9	0.326
10	0.247

2.12 ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	SEMINAL VESICLES (%)
--------	-------------------------

GROUP 3 (300 MG/KG)

11	0.217
12	0.192
13	0.226
14	0.318
15	0.234

GROUP 4 (1000 MG/KG)

16	0.218
17	0.201
18	0.216
19	0.230
20	0.176

20Dec16 13h37

2.12 ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)
GROUP 1 (CONTROL)				
21	178	1.77	0.545	4.32
22	186	1.87	0.550	4.99
23	180	1.83	0.545	4.75
24	168	1.72	0.555	4.29
25	167	1.81	0.515	4.93
GROUP 2 (100 MG/KG)				
26	179	1.70	0.530	4.71
27	182	1.77	0.615	5.41
28	168	1.76	0.550	4.36
29	166	1.74	0.540	4.68
30	169	1.81	0.565	4.49
GROUP 3 (300 MG/KG)				
31	169	1.76	0.535	4.70
32	184	1.85	0.575	4.90
33	181	1.76	0.545	4.76
34	184	1.85	0.590	4.85
35	187	1.85	0.590	5.35
GROUP 4 (1000 MG/KG)				
36	198	1.84	0.590	6.21
37	186	1.79	0.675	6.95
38	171	1.78	0.535	4.92
39	170	1.77	0.570	5.19
40	185	1.80	0.610	5.54

FEMALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 1 (CONTROL)				
21	0.010	0.410	1.31	0.060
22	0.013	0.380	1.30	0.065
23	0.013	0.470	1.34	0.055
24	0.013	0.350	1.24	0.065
25	0.014	0.305	1.47	0.070
GROUP 2 (100 MG/KG)				
26	0.012	0.390	1.50	0.055
27	0.013	0.430	1.45	0.060
28	0.013	0.310	1.28	0.075
29	0.011	0.435	1.33	0.035
30	0.011	0.345	1.19	0.070
GROUP 3 (300 MG/KG)				
31	0.012	0.320	1.19	0.060
32	0.016	0.420	1.33	0.065
33	0.010	0.350	1.34	0.055
34	0.011	0.305	1.33	0.065
35	0.014	0.420	1.37	0.070
GROUP 4 (1000 MG/KG)				
36	0.014	0.410	1.37	0.060
37	0.011	0.335	1.57	0.065
38	0.010	0.315	1.16	0.055
39	0.015	0.430	1.30	0.055

2.12 ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	THYROIDS (GRAM)	THYMUS (GRAM)	KIDNEYS (GRAM)	ADRENALS (GRAM)
GROUP 4 (1000 MG/KG)				
40	0.011	0.365	1.24	0.060
FEMALES				
END OF TREATMENT				
ANIMAL	SPLEEN (GRAM)	OVARIES (GRAM)	UTERUS (GRAM)	
GROUP 1 (CONTROL)				
21	0.330	0.115	0.315	
22	0.350	0.110	0.330	
23	0.400	0.115	0.365	
24	0.350	0.105	0.360	
25	0.315	0.130	0.390	
GROUP 2 (100 MG/KG)				
26	0.345	0.145	0.730	
27	0.370	0.120	0.465	
28	0.325	0.125	0.360	
29	0.315	0.110	0.285	
30	0.435	0.115	0.740	
GROUP 3 (300 MG/KG)				
31	0.290	0.105	0.325	
32	0.425	0.135	0.380	
33	0.385	0.140	0.385	
34	0.350	0.105	0.425	
35	0.435	0.145	0.540	
GROUP 4 (1000 MG/KG)				
36	0.405	0.135	0.355	
37	0.405	0.135	0.535	
38	0.360	0.115	0.770	
39	0.385	0.110	0.395	
40	0.345	0.145	0.550	

20Dec16 13h37

2.12 ORGAN/BODY WEIGHT RATIOS (%)**FEMALES****END OF TREATMENT**

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)
GROUP 1 (CONTROL)				
21	178	1.00	0.307	2.43
22	186	1.00	0.295	2.68
23	180	1.02	0.304	2.65
24	168	1.02	0.331	2.56
25	167	1.08	0.309	2.95
GROUP 2 (100 MG/KG)				
26	179	0.95	0.296	2.63
27	182	0.97	0.339	2.98
28	168	1.05	0.328	2.60
29	166	1.05	0.326	2.83
30	169	1.07	0.334	2.66
GROUP 3 (300 MG/KG)				
31	169	1.04	0.316	2.77
32	184	1.01	0.313	2.67
33	181	0.97	0.301	2.62
34	184	1.01	0.321	2.64
35	187	0.99	0.316	2.87
GROUP 4 (1000 MG/KG)				
36	198	0.93	0.298	3.14
37	186	0.96	0.363	3.74
38	171	1.04	0.312	2.87
39	170	1.04	0.335	3.04
40	185	0.97	0.330	3.00
FEMALES				
END OF TREATMENT				
ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 1 (CONTROL)				
21	0.006	0.231	0.73	0.034
22	0.007	0.204	0.70	0.035
23	0.007	0.262	0.74	0.031
24	0.008	0.208	0.74	0.039
25	0.008	0.183	0.88	0.042
GROUP 2 (100 MG/KG)				
26	0.007	0.218	0.83	0.031
27	0.007	0.237	0.80	0.033
28	0.008	0.185	0.76	0.045
29	0.007	0.263	0.80	0.021
30	0.006	0.204	0.70	0.041
GROUP 3 (300 MG/KG)				
31	0.007	0.189	0.70	0.035
32	0.009	0.229	0.72	0.035
33	0.006	0.193	0.74	0.030
34	0.006	0.166	0.72	0.035
35	0.007	0.225	0.73	0.038
GROUP 4 (1000 MG/KG)				
36	0.007	0.207	0.69	0.030
37	0.006	0.180	0.85	0.035
38	0.006	0.184	0.67	0.032
39	0.009	0.252	0.76	0.032

20Dec16 13h37

2.12 ORGAN/BODY WEIGHT RATIOS (%)**FEMALES****END OF TREATMENT**

ANIMAL	THYROIDS (%)	THYMUS (%)	KIDNEYS (%)	ADRENALS (%)
GROUP 4 (1000 MG/KG)				
40	0.006	0.197	0.67	0.032
FEMALES				
END OF TREATMENT				
ANIMAL	SPLEEN (%)	OVARIES (%)	UTERUS (%)	
GROUP 1 (CONTROL)				
21	0.186	0.065	0.177	
22	0.188	0.059	0.177	
23	0.223	0.064	0.203	
24	0.208	0.063	0.214	
25	0.189	0.078	0.234	
GROUP 2 (100 MG/KG)				
26	0.193	0.081	0.408	
27	0.204	0.066	0.256	
28	0.194	0.075	0.215	
29	0.190	0.066	0.172	
30	0.257	0.068	0.438	
GROUP 3 (300 MG/KG)				
31	0.171	0.062	0.192	
32	0.231	0.073	0.207	
33	0.212	0.077	0.212	
34	0.190	0.057	0.231	
35	0.233	0.078	0.290	
GROUP 4 (1000 MG/KG)				
36	0.205	0.068	0.179	
37	0.218	0.073	0.288	
38	0.210	0.067	0.449	
39	0.226	0.065	0.232	
40	0.187	0.078	0.297	

20Dec16 13h37

2.13 KEY TO MISSING VALUES AND REMARKS CLINICAL LABORATORY INVESTIGATIONS

End of Treatment

Haematology:		
Animal(s):		
All animals		Samples were frozen on dry-ice prior to analysis on the STA Compact
2, 4, 10, 19, 33		Samples were not checked for Platelet clots; haematology results should be interpreted with caution
1	---	= Value for APTT could not be reproduced
2, 4, 24, 26, 36		Differential leucocyte count was also performed manually because of an abnormal plot in the automated count and these results are reported

Clinical Biochemistry:

All animals		Samples were stored at ≤ -75°C prior to analysis on the AU400
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APPENDIX 3
PHASE REPORT FORMULATION ANALYSIS

TABLE OF CONTENTS

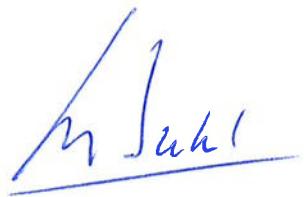
LIST OF TABLES	2
1. REPORT APPROVAL.....	3
2. SUMMARY	4
3. INTRODUCTION	5
3.1. Study schedule analytical phase.....	5
3.2. Purpose of the study.....	5
4. MATERIALS AND METHODS	5
4.1. Reagents	5
4.2. Study samples	5
4.3. Analytical method.....	5
4.3.1. Analytical conditions	5
4.3.2. Preparation of solutions	6
4.3.3. Sample injections	6
4.4. Electronic systems for data acquisition.....	6
4.5. Formulas	7
4.6. Specifications.....	7
5. RESULTS	8
5.1. Calibration curves	8
5.2. Samples	8
5.2.1. QC samples	8
5.2.2. Study samples	8

LIST OF TABLES

Table 1	QC samples	9
Table 2	Accuracy and homogeneity test.....	9

1. REPORT APPROVAL

Charles River Den Bosch



Signature:

Name: M.J.C. Brekelmans, MSc.

Title: Principal Scientist
Analytical Chemistry

Date:.....

2. SUMMARY

The purpose of this part of the study was to determine the accuracy of preparation, homogeneity and stability of the test item in formulations.

Accuracy of preparation

The concentrations analysed in the formulations of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%).

No test item was detected in the Group 1 formulation.

Homogeneity

The formulations of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation $\leq 10\%$).

3. INTRODUCTION

3.1. Study schedule analytical phase

Experimental starting date 20 October 2016
Experimental completion date 20 October 2016

3.2. Purpose of the study

The purpose of the analytical phase was to determine the accuracy of preparation, homogeneity and stability of the test item in formulations.

4. MATERIALS AND METHODS

4.1. Reagents

Water Tap water purified by a Milli-Q water purification system (Millipore, Bedford, MA, USA)
Methanol Biosolve, Valkenswaard, The Netherlands

All reagents were of analytical grade, unless specified otherwise.

4.2. Study samples

Accuracy and homogeneity were determined for formulations prepared for use during treatment.

Duplicate samples (approximately 500 mg), which were taken from the formulations using a pipette, were accurately weighed into volumetric flasks of 50 mL. For determination of accuracy, samples were taken at middle position (50% height) or at top, middle and bottom position (90%, 50% and 10% height). The samples taken at 90%, 50% and 10% height were also used for the determination of the homogeneity of the formulations.

The volumetric flasks were filled up to the mark with methanol. The solutions were further diluted to obtain an end solution of methanol and concentrations within the calibration range.

4.3. Analytical method

4.3.1. Analytical conditions

Analysis was based on the analytical method validated for the test item in project 514869. Several peaks were observed in the chromatogram of the test item containing samples. The peak area of the peak with a retention time of 1.9 minutes was used as response in the calculations.

Instrument	Acquity UPLC system (Waters, Milford, MA, USA)
Detector	Acquity UPLC TUV detector (Waters)
Column	Acquity UPLC HSS Cyano, 100 mm × 2.1 mm i.d., dp = 1.8 µm (Waters)
Column temperature	40°C ± 1°C
Injection volume	1 µL
Mobile phase	70/30 (v/v) methanol/water
Flow	0.4 mL/min

UV detection 210 nm

4.3.2. Preparation of solutions

Stock and spiking solutions

Stock solutions of the test item were prepared in methanol at a concentration of 4000 mg/L. For spiking, a stock solution or the test item itself were used

Calibration solutions

Solutions with the test item in the concentration range of 8 - 250 mg/L were prepared in methanol from two stock solutions.

Quality control (QC) samples

Approximately 500 mg blank vehicle was spiked with the test item at a target concentration of 1 or 203 mg/g. The QC samples were treated similarly as the study samples (see paragraph 4.2 ‘Study samples’).

4.3.3. Sample injections

Calibration solutions were injected in duplicate. Study samples and QC samples were analysed by single injection.

4.4. Electronic systems for data acquisition

System control, data acquisition and data processing were performed using the following program:

- Empower 3 database version 7.21 (Waters, Milford, MA, USA).

Temperature, relative humidity and/or atmospheric pressure during sample storage and/or performance of the studies was monitored continuously using the following program:

- REES Centron Environmental Monitoring system version SQL 2.0 (REES Scientific, Trenton, NJ, USA).

4.5. Formulas

Response (R) Peak area test item [units]

$$R = a C_N + b$$

where:

C_N = nominal concentration [mg/L]

a = slope [units \times L/mg]

b = intercept [units]

$$C_A = \frac{(R - b)}{a} \times \frac{V \times d}{w} \text{ [mg/g]}$$

where:

w = weight sample [mg]

V = volume volumetric flask [mL]

d = dilution factor

$$\frac{C_A}{C_N} \times 100 \text{ [%]}$$

where:

C_N = nominal concentration [mg/g]

$$\frac{C_A}{C_T} \times 100 \text{ [%]}$$

where:

C_T = target concentration [mg/g]

4.6. Specifications

Preparation of formulations was considered acceptable if the mean accuracy was in the range 85-115% of the target concentration and was considered homogeneous if the coefficient of variation was $\leq 10\%$.

5. RESULTS

5.1. Calibration curves

A calibration curve was constructed using five concentrations. For each concentration, two responses were used. Linear regression analysis was performed using the least squares method with a 1/concentration² weighting factor. The coefficient of correlation (r) was > 0.99.

5.2. Samples

5.2.1. QC samples

The results of the QC samples are given in [Table 1](#).

The mean accuracies of the QC samples were within the criterion range of 85-115%. It demonstrated that the analytical method was adequate for the determination of the test item in the study samples.

5.2.2. Study samples

The results of the study samples are given in [Table 2](#).

Accuracy of preparation

In the Group 1 formulation, no test item was detected.

The concentrations analysed in the formulations of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. mean accuracies between 85% and 115%).

Homogeneity

The formulations of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation ≤ 10%).

Table 1
QC samples

Date of analysis	Concentration [mg/g]			Accuracy [%]	
	Target	Nominal	Analysed	Individual	Mean
20 Oct 2016	1	0.974	0.967	99	97
		1.01	0.954	95	
20 Oct 2016	203	215	222	103	104
		204	212	104	

Table 2
Accuracy and homogeneity test

Date of analysis	20 Oct 2016
------------------	-------------

Group	Sample position	Concentration		Accuracy		Homogeneity (coefficient of variation) [%]
		[mg/g]		%		
		Target	Analysed	Individual	Mean	
1	50% height	0.00	n.d.	n.a.	n.a.	n.a.
		0.00	n.d.	n.a.		
2	90% height	20.0	20.6	103	104	1.4
		20.0	20.6	103		
	50% height	20.0	20.7	103		
		20.0	20.7	103		
	10% height	20.0	21.3	107		
		20.0	21.0	105		
3	50% height	60.2	66.1	110	109	n.a.
		60.2	64.7	107		
4	90% height	203	212	105	104	1.3
		203	216	107		
	50% height	203	211	104		
		203	211	104		
	10% height	203	208	103		
		203	209	103		

n.d. Not detected.

n.a. Not applicable.

APPENDIX 4
PHASE REPORT HISTOPATHOLOGY

TABLE OF CONTENTS

1.	SUMMARY	3
2.	INTRODUCTION	4
3.	STUDY DESIGN	4
4.	METHODS	4
4.1.	Macroscopic Examination	4
4.2.	Organ Weights	5
4.3.	Microscopic Examination	5
4.4.	Internal Peer Review	6
5.	RESULTS	7
5.1.	Mortality	7
5.2.	Clinical Pathology	7
5.3.	Macroscopic Findings	7
5.4.	Organ Weights	7
5.5.	Microscopic Findings	7
6.	DISCUSSION	9
7.	CONCLUSIONS	9
8.	REPORT AUTHENTICATION	10

LIST OF APPENDICES**APPENDIX 1 HISTOPATHOLOGY TABLES**

1. SUMMARY

Pathomorphologic examination was performed on 40 Wistar (Han) rats (20 males, 20 females) which had been subjected to a 28 day oral (gavage) toxicity study with the test item **MLA-3202**.

The rats were assigned to four dose groups, each containing 5 males and 5 females. The test item was administered once daily by gavage at doses of 100, 300 and 1000 mg/kg/day (dose Groups 2, 3 and 4 respectively) for 28 days. The rats of the control Group 1 received the vehicle, water (Elix), alone.

At the end of the treatment period all rats from all Groups were killed and subjected to complete necropsies. Histopathologic examination was performed on an extensive list of organs and tissues from all Group 1 and 4 animals as well as the spleen from all males and liver of all females from Group 2 and 3 rats and all organs with macroscopic findings from all rats.

There were no unscheduled deaths.

There were no test item-related macroscopic findings.

There was a test item-related decrease in spleen weight (absolute) in males at 1000 mg/kg/day. The microscopic correlate to this was decreased hematopoiesis. The other organ weights were in line with the decrease in body weight.

In females there was a test item-related increase in liver weight (absolute and relative to body weight) at 1000 mg/kg/day. The microscopic correlate to this was hepatocellular hypertrophy.

Test item-related microscopic findings were present in the

Spleen, a decreased incidence and severity of *extramedullary hematopoiesis* was present in males treated at 1000 mg/kg/day.

Liver, *hepatocellular hypertrophy* was present in females treated at 1000 mg/kg/day at minimal degree.

These findings, in the absence of any accompanying findings were considered to be non-adverse.

There were non-adverse test item-related morphologic alterations in the male **spleen** and female **liver** of Wistar (Han) rats after treatment with **MLA-3202** for at least 28 days at 1000 mg/kg/day.

2. INTRODUCTION

The nature and purpose of this toxicity study was to assess the toxic potential of the test item when administered to rats by daily oral gavage for a period of 28 days.

This pathology report addresses the anatomical pathology endpoints of the study. It is based on the study plan and any study plan amendment.

This study should provide part of a rational basis for toxicological risk assessment in man. The oral route was selected as it is a possible route of human exposure during manufacture, handling or use of the test item.

3. STUDY DESIGN

Male and female Wistar (Han) rats, approximately 6 weeks of age on study Day 1, were administered MLA-3202 via oral gavage daily for at least 28 consecutive days as indicated in the following table.

Group Number	Dose level (mg/kg/day)	Number of animals		Animal numbers	
		Males	Females	Males	Females
1	0 (vehicle) ^a	5	5	1-5	21-25
2	100	5	5	6-10	26-30
3	300	5	5	11-15	31-35
4	1000	5	5	16-20	36-40

^a The vehicle was water (Elix).

4. METHODS

4.1. Macroscopic Examination

Complete postmortem examinations were performed on all animals. Animals were anesthetized using isoflurane and subsequently exsanguinated. At the time of necropsy, the following tissues and organs were collected and placed in 10% neutral-buffered formalin fixative unless otherwise noted:

Identification marks: not processed	Ovaries
Adrenal glands	(Pancreas)
(Aorta)	Peyer's patches [jejunum, ileum] if detectable
Brain -cerebellum, midbrain, cortex (7 levels)	(Pituitary gland)
Caecum	(Preputial gland)
Cervix	Prostate gland
(Clitoral gland)	Rectum
Colon	(Salivary glands - mandibular, sublingual)
Duodenum	Sciatic nerve
Epididymides *	Seminal vesicles including coagulating gland
Eyes (including optic nerve [if detectable] and harderian gland) *	Skeletal muscle
(Female mammary gland area)	(Skin)
Femur including joint	Spinal cord -cervical, midthoracic, lumbar
Heart	Spleen
Ileum	Sternum with bone marrow
Jejunum	Stomach
Kidneys	Testes *
(Larynx)	Thymus
(Lacrimal gland, exorbital)	Thyroid including parathyroid [if detectable]
Liver	(Tongue)
Lung, infused with formalin	Trachea
	Urinary bladder

Lymph nodes - mandibular, mesenteric (Nasopharynx) (Oesophagus)	Uterus Vagina All gross lesions
---	---------------------------------------

Tissues/organs mentioned in parentheses were not examined by the pathologist.

* Initially fixed in modified Davidson's solution.

4.2. Organ Weights

The following organ weights (and terminal body weight) were recorded from all animals at the scheduled necropsy:

Adrenal glands	Spleen
Brain	Testes
Epididymides	Thymus
Heart	Uterus (including cervix)
Kidneys	Prostate
Liver	Seminal vesicles including coagulating glands
Ovaries	Thyroid including parathyroid

Paired organs were weighed together. Absolute organ weights were reported and organ to terminal body weights were calculated and presented in the main study report.

In the discussion of organ weights, statistical significance refers to the $p < 0.05$ level. The discussion of organ weights refers to group mean values unless stated otherwise.

4.3. Microscopic Examination

Microscopic examination of routinely prepared hematoxylin-eosin stained paraffin sections was performed on all tissues collected at necropsy (with exceptions as indicated on the tissue list above) from all control group and 1000 mg/kg/day treated animals, slides of the spleen of all males and the liver of all females treated at 100 and 300 mg/kg/day. Gross lesions were examined from all animals and correlated to microscopic findings if possible.

The animal data and macroscopic findings were electronically transferred from the necropsy raw data files of ToxData system® into the computer system PathData®. Stained histologic sections were examined by light microscopy in the period 05 December 2016 – 11 January 2017 and the microscopic findings were recorded by the undersigned pathologist using online input under pathology number 41639 JOL.

Severity grades were assigned to non-neoplastic histopathologic diagnoses, as presented in the following table. Severity grades were assigned based on the severity of alterations in the examined histologic sections and may not reflect the overall severity of the pathologic process in the entire tissue, organ, or animal. The PathData® histopathology tables contain all of the recorded data and serve as the basis for this narrative report.

In the separate pathology tables file, all macroscopic and microscopic findings are given for each animal in text form under "Text of Gross and Microscopic Findings". The incidence of microscopic findings is also presented in tabular form: "Incidence table – Selected findings with grades" and "Incidence table - all microscopic findings". Incidence tables were created by computer.

Histopathological changes were described according to distribution, severity and morphological character.

Severity scores were assigned as follows:

Present	Finding present, grading not scored.
Grade 1	Minimal/very few/very small.
Grade 2	Slight/few/small.
Grade 3	Moderate/moderate number/moderate size.
Grade 4	Marked/many/large.
Grade 5	Massive/extensive number/extensive size.
N.A.D.	No Abnormality Detected

4.4. Internal Peer Review

Pathology findings were subjected to an internal review conducted by Hetty van den Brink-Knol, DVM (Dutch CRP/TP Certified Toxicologic Pathologist). Following the peer review, a consensus was reached between the study pathologist and the peer review pathologist with regard to diagnoses and interpretation. Histopathology data entries in PathData® and pathology data presented in the pathology report reflect this consensus.

5. RESULTS

5.1. Mortality

There were no premature decedents in the study.

5.2. Clinical Pathology

Clinical pathology data were evaluated and discussed by the study pathologist and the study director. Clinical pathology results are presented in the main toxicology report.

5.3. Macroscopic Findings

There were no test item-related gross observations.

All of the recorded macroscopic findings were within the range of background gross observations encountered in rats of this age and strain.

5.4. Organ Weights

Test item-related lower **spleen** weights (absolute) were noted in the 1000 mg/kg/day males and higher **liver** weights were noted in the 1000 mg/kg/day females as shown in text table 1.

For males, the other organ weights were in line with the decrease in body weight.

Text Table 1
Mean Percent Organ Weight Differences from Control Groups

Dose level (mg/kg/day):	Males		
	100	300	1000
SPLEEN			
Absolute	-12	-10	-24**
Relative to body weight	-2	-7	-13
Females			
LIVER			
Absolute	2	6	24**
Relative to body weight	3	2	19**

*: P<0.05, **: P<0.01

There were no other test item-related organ weight changes.

5.5. Microscopic Findings

Test item-related microscopic findings after treatment with MLA-3202 were noted in the **spleen** of the 1000 mg/kg/day group males and the **liver** of the 1000 mg/kg/day females and are summarized in text table 2.

Text Table 2.
Summary Test Item-Related Microscopic Findings

Dose level (mg/kg/day):	Males			
	0	100	300	1000
SPLEEN ^a	5	5	5	5
<i>Extramedullary hematopoiesis</i>				
Minimal	5	4	3	-
Slight	-	1	-	-
LIVER ^a	5	5	5	5
<i>Hepatocellular hypertrophy</i>				
Minimal	-	-	-	4

^a = Number of tissues examined from each group.

Spleen, the normally occurring extramedullary hematopoiesis was not detectable in males treated at 1000 mg/kg/day.

Liver, hepatocellular hypertrophy was present in females treated at 1000 mg/kg/day at minimal degree.

The remainder of the recorded microscopic findings were within the range of background pathology encountered in rats of this age and strain. There was no test item-related alteration in the prevalence, severity, or histologic character of those incidental tissue alterations.

6. DISCUSSION

Relationships were suspected between gross necropsy, organ weight and histopathology observations, as presented in Text Table 3. These proposed relationships were based on subjective interpretation rather than a statistical analysis of correlation.

Text Table 3.
Correlations of Selected Observations

Organ	Organ Weight	Histopathology
Spleen	↓	Decreased hematopoiesis
Liver	↑	Hepatocellular hypertrophy

Spleen, the decreased hematopoiesis in males treated at 1000 mg/kg/day, in the absence of any other indicator of toxicity was considered non-adverse.

The minimal *hepatocellular hypertrophy* of the **liver** as recorded in the females at 1000 mg/kg/day, in the absence of any degenerative findings was considered to be a non-adverse finding (Kerlin et al., 2016).

7. CONCLUSIONS

There were non-adverse test item-related morphologic alterations in the male **spleen** and female **liver** of Wistar (Han) rats after treatment with **MLA-3202** for at least 28 days at 1000 mg/kg/day.

8. REFERENCES

- Kerlin, R., Bolon, B., Burkhardt, J., Francke, S., Greaves, P., Meador, V., Popp, P. (2016). Scientific and Regulatory Policy Committee: Recommended (“Best”) Practice for Determining, Communicating, and Using Adverse Effect Data from Nonclinical Studies. *Toxicol. Pathol.* **44**(2), 147-162.

Final Report

Page 10
Test Facility Study No. 514867
Pathology No. 41639

9. REPORT AUTHENTICATION

I, the undersigned, was responsible for the histopathology evaluation and reporting of the pathology data. The histopathology data in this report were compiled by me, and they reflect accurately the primary data records. Histopathology tables were created in PathData® under number 41639 JOL.

FINAL histopathology tables generated 27-February-2017

Project 514867 Pathology Report

Report and Histopathology Tables Submitted By:



27-Feb-2017

Joost Lensen, PhD

Dutch CRP/TP Certified Toxicologic Pathologist
Study Pathologist

Date

APPENDIX 1
HISTOPATHOLOGY TABLES

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TABLE OF CONTENTS

	PAGE :
EXPLANATION OF CODES AND SYMBOLS	1
SUMMARY TABLES	
SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX	
NECROPSY STATUS: TERMINAL SACRIFICE GROUP (K0)	
Incidence table - Selected findings with grades	2
NUMBER OF ANIMALS WITH	
MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX	
STATUS AT NECROPSY: K0	
Incidence table - All microscopic findings	3 - 12
INDIVIDUAL ANIMAL DATA	
TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)	13 - 20
ANIMAL HEADING DATA DOSE GROUP 01	21
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 01	22 - 32
ANIMAL HEADING DATA DOSE GROUP 02	33
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 02	34 - 40
ANIMAL HEADING DATA DOSE GROUP 03	41
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 03	42 - 47
ANIMAL HEADING DATA DOSE GROUP 04	48
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 04	49 - 60

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

M = Male animal
F = Female animal
KO = Terminal sacrifice group

CODES AND SYMBOLS USED AT ORGAN LEVEL:

G = Gross observation checked off histologically
0 = Tissue not present for histologic examination
' = Histologic examination not required
+ = Organ examined, findings present
- = Organ examined, no pathologic findings noted (AOFT only)
(= Only one of paired organs examined/present

CODES AND SYMBOLS USED AT FINDING LEVEL:

GRADE 1 = Minimal / very few / very small
GRADE 2 = Slight / few / small
GRADE 3 = Moderate / moderate number / moderate size
GRADE 4 = Marked / many / large
GRADE 5 = Massive / extensive number / extensive size
P = Finding present, severity not scored
(= Finding unilateral in paired organs

TEST ITEM : MLA-3202
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FINALIZED : 27-FEB-17
PathData®System V6.2e2

SUMMARY INCIDENCE OF GRADING BY ORGAN/GROUP/SEX Necropsy Status: TERMINAL SACRIFICE GROUP (K0) Incidence table - Selected findings with grades									
Sex	Males				Females				
	Dose Group No. Animals per Dose Group	01 5	02 5	03 5	04 5	01 5	02 5	03 5	04 5
SPLEEN	No.Examined	5	5	5	5	5	-	-	5
- Hematopoiesis	GRADE 1	5	4	3	-	3	-	-	2
	GRADE 2	-	1	-	-	-	-	-	1
	TOTAL AFFECTED	5	5	3	-	3	-	-	3
	MEAN GRADE/TISS.AFFECTED	1.0	1.2	1.0	-	1.0	-	-	1.3
LIVER	No.Examined	5	-	-	5	5	5	5	5
- Hypertrophy	GRADE 1	-	-	-	-	-	-	-	4
	TOTAL AFFECTED	-	-	-	-	-	-	-	4
	MEAN GRADE/TISS.AFFECTED	-	-	-	-	-	-	-	1.0

Group 01, CONTROL, males: MLA-3202 (0 mg/kg); females: MLA-3202 (0 mg/kg)

Group 02, 100 MG/KG, males: MLA-3202 (100 mg/kg); females: MLA-3202 (100 mg/kg)

Group 03, 300 MG/KG, males: MLA-3202 (300 mg/kg); females: MLA-3202 (300 mg/kg)

Group 04, 1000 MG/KG, males: MLA-3202 (1000 mg/kg); females: MLA-3202 (1000 mg/kg)

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PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
BRAIN :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, CERVIC. :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, THORAC. :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, LUMBAR :	5	-	-	5	
N.A.D. :	5	-	-	5	
SCIATIC NERVE, LEFT :	5	-	-	5	
N.A.D. :	5	-	-	5	
EYES :	5	-	-	5	
N.A.D. :	5	-	-	5	
THYMUS :	5	-	-	5	
N.A.D. :	4	-	-	4	

- Lymphocytolysis :	1	-	-	1	
Grade 1:	1	-	-	1	
MANDIB. LYMPH NODES :	5	-	-	5	
N.A.D. :	5	-	-	5	
ADRENAL GLANDS :	5	-	-	5	
N.A.D. :	5	-	-	5	
THYROID GLAND :	5	-	-	5	
N.A.D. :	5	-	-	5	

Group 01, CONTROL, males: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, males: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, males: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, males: MLA-3202 (1000 mg/kg)

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PATHOL. NO.: 41639 JOL
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PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
PARATHYROID GLANDS :	5	-	-	5	
N.A.D. :	5	-	-	5	
LUNG :	5	-	-	5	
N.A.D. :	3	-	-	2	
.....					
- Inflamm. peribronch.:	2	-	-	3	
Grade 1:	2	-	-	3	
Grade 2:	-	-	-	-	
TRACHEA :	5	-	-	5	
N.A.D. :	5	-	-	5	
SKELETAL MUSCLE :	5	-	-	5	
N.A.D. :	5	-	-	5	
HEART :	5	-	-	5	
N.A.D. :	4	-	-	5	
.....					
- Infiltrate inflamm.:	1	-	-	-	
Grade 1:	1	-	-	-	
SPLEEN :	5	5	5	5	
N.A.D. :	-	-	2	5	
.....					
- Hematopoiesis extra.:	5	5	3	-	
Grade 1:	5	4	3	-	
Grade 2:	-	1	-	-	
- Pigmentation, hemos.:	-	-	1	-	
Grade 1:	-	-	1	-	

Group 01, CONTROL, males: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, males: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, males: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, males: MLA-3202 (1000 mg/kg)

TEST ITEM : MLA-3202
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PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
LIVER :	5	-	-	5	
N.A.D. :	1	-	-	2	
.....					
- Infiltrate inflamm. :	4	-	-	3	
Grade 1:	4	-	-	3	
URINARY BLADDER :	5	-	-	5	
N.A.D. :	5	-	-	5	
KIDNEYS :	5	-	-	5	
N.A.D. :	2	-	-	3	
.....					
- Infiltrate inflamm. :	-	-	-	2	
Grade 1:	-	-	-	2	
- Hyaline droplet acc.:	1	-	-	2	
Grade 1:	-	-	-	2	
Grade 2:	1	-	-	-	
- Basophilia, tubule :	2	-	-	1	
Grade 1:	2	-	-	1	
STOMACH :	5	-	-	5	
N.A.D. :	5	-	-	5	
DUODENUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
JEJUNUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
ILEUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
PEYER'S PATCHES :	5	-	-	5	
N.A.D. :	5	-	-	5	

Group 01, CONTROL, males: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, males: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, males: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, males: MLA-3202 (1000 mg/kg)

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PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
CECUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
COLON :	5	-	-	5	
N.A.D. :	5	-	-	5	
RECTUM :	4	-	-	5	
N.A.D. :	4	-	-	5	
MESENT. LYMPH NODE :	5	-	-	5	
N.A.D. :	4	-	-	5	
.....					
- Incr. macrophages :	1	-	-	-	
Grade 1:	1	-	-	-	
SEMINAL VESICLES :	5	-	-	5	
N.A.D. :	5	-	-	5	
COAGULATING GLANDS :	5	-	-	5	
N.A.D. :	5	-	-	5	
PROSTATE GLAND :	5	-	-	5	
N.A.D. :	2	-	-	5	
.....					
- Infiltrate inflamm. :	3	-	-	-	
Grade 1:	2	-	-	-	
Grade 2:	1	-	-	-	
TESTES :	5	-	-	5	
N.A.D. :	5	-	-	3	
.....					
- Atrophy, tubular :	-	-	-	1	
Grade 5:	-	-	-	1	
- Vacuolation, tubular:	-	-	-	1	
Grade 1:	-	-	-	1	

Group 01, CONTROL, males: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, males: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, males: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, males: MLA-3202 (1000 mg/kg)

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PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :	MALE			
DOSE GROUP:	01	02	03	04
NO. ANIMALS:	5	5	5	5
EPIDIDYMIDES :	5	1	1	5
N.A.D. :	3	-	-	4

- Infiltrate inflamm. :	2	-	1	-
Grade 1:	2	-	-	-
Grade 2:	-	-	1	-
- Cell debris, luminal:	-	-	-	1
Grade 2:	-	-	-	1
- Reduced sperm, lum. :	-	-	-	1
Grade 5:	-	-	-	1
- Sperm granuloma :	-	1	1	-
Grade 3:	-	-	1	-
Grade 4:	-	1	-	-
BONE, STERNUM :	5	-	-	5
N.A.D. :	5	-	-	5
BONE MARROW, STERNUM :	5	-	-	5
N.A.D. :	5	-	-	4

- Increased adipocytes:	-	-	-	1
Grade 1:	-	-	-	1
BONE, FEMUR :	5	-	-	5
N.A.D. :	5	-	-	5
JOINT, KNEE, LEFT :	5	-	-	5
N.A.D. :	5	-	-	5

Group 01, CONTROL, males: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, males: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, males: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, males: MLA-3202 (1000 mg/kg)

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
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PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
BRAIN :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, CERVIC. :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, THORAC. :	5	-	-	5	
N.A.D. :	5	-	-	5	
SPINAL CORD, LUMBAR :	4	-	-	5	
N.A.D. :	4	-	-	5	
SCIATIC NERVE, LEFT :	5	-	-	5	
N.A.D. :	5	-	-	5	
EYES :	5	-	-	5	
N.A.D. :	5	-	-	5	
THYMUS :	5	-	-	5	
N.A.D. :	4	-	-	5	

- Lymphocytolysis :	1	-	-	-	
Grade 1:	1	-	-	-	
MANDIB. LYMPH NODES :	5	-	-	5	
N.A.D. :	5	-	-	5	
ADRENAL GLANDS :	5	2	-	5	
N.A.D. :	5	1	-	5	

- Vacuol. fasciculata :	-	1	-	-	
Grade 1:	-	1	-	-	

Group 01, CONTROL, females: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, females: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, females: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, females: MLA-3202 (1000 mg/kg)

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
THYROID GLAND :	5	-	-	5	
N.A.D. :	3	-	-	3	
.....					
- Hypertrophy foll. c.:	2	-	-	2	
Grade 1:	2	-	-	2	
PARATHYROID GLANDS :	5	-	-	5	
N.A.D. :	5	-	-	5	
LUNG :	5	-	-	5	
N.A.D. :	1	-	-	1	
.....					
- Alveolar macrophages:	1	-	-	-	
Grade 1:	1	-	-	-	
- Inflamm. peribranch.:	4	-	-	4	
Grade 1:	4	-	-	3	
Grade 2:	-	-	-	1	
- Osseus metaplasia :	-	-	-	1	
Grade 1:	-	-	-	1	
TRACHEA :	5	-	-	5	
N.A.D. :	3	-	-	5	
.....					
- Infiltrate inflamm.:	1	-	-	-	
Grade 1:	1	-	-	-	
- Ectasia subm. glands:	1	-	-	-	
Grade 1:	1	-	-	-	
SKELETAL MUSCLE :	5	-	-	5	
N.A.D. :	5	-	-	5	
HEART :	5	-	-	5	
N.A.D. :	5	-	-	5	

Group 01, CONTROL, females: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, females: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, females: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, females: MLA-3202 (1000 mg/kg)

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
SPLEEN :	5	-	-	5	
N.A.D. :	1	-	-	1	
.....					
- Hematopoiesis extra.:	3	-	-	3	
Grade 1:	3	-	-	2	
Grade 2:	-	-	-	1	
- Pigmentation, hemos.:	2	-	-	2	
Grade 1:	2	-	-	2	
LIVER :	5	5	5	5	
N.A.D. :	-	-	-	1	
.....					
- Infiltrate inflamm.:	5	5	5	3	
Grade 1:	5	5	5	3	
- Hypertrophy hepatoc.:	-	-	-	4	
Grade 1:	-	-	-	4	
URINARY BLADDER :	5	-	-	5	
N.A.D. :	5	-	-	5	
KIDNEYS :	5	-	-	5	
N.A.D. :	4	-	-	5	
.....					
- Infiltrate inflamm.:	1	-	-	-	
Grade 1:	1	-	-	-	
STOMACH :	5	-	-	5	
N.A.D. :	4	-	-	5	
.....					
- Cyst(s) :	1	-	-	-	
Grade 1:	1	-	-	-	
DUODENUM :	5	-	-	5	
N.A.D. :	5	-	-	5	

Group 01, CONTROL, females: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, females: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, females: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, females: MLA-3202 (1000 mg/kg)

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
JEJUNUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
ILEUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
PEYER'S PATCHES :	5	-	-	5	
N.A.D. :	5	-	-	5	
CECUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
COLON :	5	-	-	5	
N.A.D. :	5	-	-	5	
RECTUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
MESENT. LYMPH NODE :	5	-	-	5	
N.A.D. :	5	-	-	5	
OVARIES :	5	-	-	5	
N.A.D. :	5	-	-	5	
UTERUS :	5	2	-	5	
N.A.D. :	5	-	-	4	
.....					
- Cyclic dilation :	-	2	-	1	
.....					
CERVIX :	5	2	-	5	
N.A.D. :	5	2	-	5	

Group 01, CONTROL, females: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, females: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, females: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, females: MLA-3202 (1000 mg/kg)

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX

STATUS AT NECROPSY: K0

Incidence table - All microscopic findings

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	5	5	5	5	
VAGINA :	5	2	-	5	
- Cycle: Proestrus :	-	1	-	1	
- Cycle: Estrus :	-	1	-	2	
- Cycle: Metestrus :	3	-	-	2	
- Cycle: Diestrus :	2	-	-	-	
BONE, STERNUM :	5	-	-	5	
N.A.D. :	5	-	-	5	
BONE MARROW, STERNUM :	5	-	-	5	
N.A.D. :	4	-	-	5	
.....					
- Increased adipocytes:	1	-	-	-	
Grade 1:	1	-	-	-	
BONE, FEMUR :	5	-	-	5	
N.A.D. :	5	-	-	5	
JOINT, KNEE, LEFT :	5	-	-	5	
N.A.D. :	5	-	-	5	

Group 01, CONTROL, females: MLA-3202 (0 mg/kg)
Group 02, 100 MG/KG, females: MLA-3202 (100 mg/kg)
Group 03, 300 MG/KG, females: MLA-3202 (300 mg/kg)
Group 04, 1000 MG/KG, females: MLA-3202 (1000 mg/kg)

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :

	1 MK0	2 MK0	3 MK0	4 MK0	5 FK0	21 FK0	22 FK0	23 FK0	24 FK0	25 FK0
BRAIN	-	-	-	-	-	-	-	-	-	-
SPINAL CORD, CERVIC.	-	-	-	-	-	-	-	-	-	-
SPINAL CORD, THORAC.	-	-	-	-	-	-	-	-	-	-
SPINAL CORD, LUMBAR	-	-	-	-	-	-	-	-	-	0
SCIATIC NERVE, LEFT	-	-	-	-	-	-	-	-	-	-
EYES	-	-	-	-	-	-	-	-	-	-
THYMUS	-	-	-	-	+	-	+	-	-	-
- Lymphocytolysis	1.	.	1.	.	.	.
MANDIB.LYMPH NODES	-	-	-	-	-	-	-	-	-	-
ADRENAL GLANDS	-	-	-	-	-	-	-	-	-	-
THYROID GLAND	-	-	-	-	-	-	-	-	+	+
- Hypertrophy foll. c.	1.	1.
PARATHYROID GLANDS	(-	-	-	-	-	(-	-	(
LUNG	-	+	-	+	-	+	+	+	-	+
- Alveolar macrophages	1.	.	.	.
- Inflamm. peribronch.	.	1.	.	1.	.	1.	1.	1.	.	1.
TRACHEA	-	-	-	-	-	+	-	-	-	+
- Infiltrate inflamm.	1.
- Ectasia subm. glands	1.
SKELETAL MUSCLE	-	-	-	-	-	-	-	-	-	-
HEART	-	-	+	-	-	-	-	-	-	-
- Infiltrate inflamm.	.	.	1.

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :

	1 MK0	2 MK0	3 MK0	4 MK0	5 FK0	21 FK0	22 FK0	23 FK0	24 FK0	25 FK0
SPLEEN	+	+	+	+	+	+	-	+	+	+
- Hematopoiesis extra.	1.	1.	1.	1.	1.	1.	.	1.	1.	.
- Pigmentation, hemos.	1.	.	1.
LIVER	+	-	+	+	+	+	+	+	+	+
- Infiltrate inflamm.	1.	.	1.	1.	1.	1.	1.	1.	1.	1.
URINARY BLADDER	-	-	-	-	-	-	-	-	-	-
KIDNEYS	-	+	+	-	+	-	-	-	-	+
- Infiltrate inflamm.	(1.
- Hyaline droplet acc.	.	.	2.
- Basophilia, tubule	.	(1.	.	.	(1.
STOMACH	-	-	-	-	-	-	-	-	-	+
- Cyst(s)	1.
DUODENUM	-	-	-	-	-	-	-	-	-	-
JEJUNUM	-	-	-	-	-	-	-	-	-	-
ILEUM	-	-	-	-	-	-	-	-	-	-
PEYER'S PATCHES	-	-	-	-	-	-	-	-	-	-
CECUM	-	-	-	-	-	-	-	-	-	-
COLON	-	-	-	-	-	-	-	-	-	-
RECTUM	0	-	-	-	-	-	-	-	-	-
MESENT. LYMPH NODE	+	-	-	-	-	-	-	-	-	-
- Incr. macrophages	1.
SEMINAL VESICLES	-	-	-	-	-	-	-	-	-	-
COAGULATING GLANDS	-	-	-	-	-	-	-	-	-	-

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :

	1 MK0	2 MK0	3 MK0	4 MK0	5 MK0	21 FK0	22 FK0	23 FK0	24 FK0	25 FK0
PROSTATE GLAND	+	+	-	+	-					
- Infiltrate inflamm.	1.	2.	.	1.	.					
TESTES	-	-	-	-	-					
EPIDIDYIMIDES	+	-	+	-	-					
- Infiltrate inflamm.	(1.	.	(1.	.	.					
OVARIES						-	-	-	-	-
UTERUS						-	-	-	-	-
CERVIX						-	-	-	-	-
VAGINA						+	+	+	+	+
- Cycle: Metestrus						.	.	P.	P.	P.
- Cycle: Diestrus						P.	P.	.	.	.
BONE, STERNUM	-	-	-	-	-	-	-	-	-	-
BONE MARROW, STERNUM	-	-	-	-	-	-	+	-	-	-
- Increased adipocytes	1.	.	.	.
BONE, FEMUR	-	-	-	-	-	-	-	-	-	-
JOINT, KNEE, LEFT	-	-	-	-	-	-	-	-	-	-

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 02, 100 MG/KG

ANIMAL NUMBER :

	6 MK0	7 MK0	8 MK0	9 MK0	10 MK0	26 FK0	27 FK0	28 FK0	29 FK0	30 FK0	
ADRENAL GLANDS	'	'	'	'	'	'	'	'	+G	'	-G
- Vacuol. fasciculata									1.		.
SPLEEN	+	+	+	+	+	'	'	'	'	'	
- Hematopoiesis extra.	1.	2.	1.	1.	1.						
LIVER	'	'	'	'	'	+	+	+	+	+	
- Infiltrate inflamm.						1.	1.	1.	1.	1.	
EPIDIDYMIDES	'	'	'	'	(+G						
- Sperm granuloma					(4.						
UTERUS						+G	'	'	'	+G	
- Cyclic dilation						P.				P.	
CERVIX						-	'	'	'	-	
VAGINA						+	'	'	'	+	
- Cycle: Proestrus						.				P.	
- Cycle: Estrus						P.				.	

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 03, 300 MG/KG

ANIMAL NUMBER :

	11 MK0	12 MK0	13 MK0	14 MK0	15 MK0	31 FK0	32 FK0	33 FK0	34 FK0	35 FK0
SPLEEN	-	+	+	-	+	'	'	'	'	'
- Hematopoiesis extra.	.	1.	1.	.	1.					
- Pigmentation, hemos.	.	.	1.	.	.					
LIVER	'	'	'	'	'	+	+	+	+	+
- Infiltrate inflamm.						1.	1.	1.	1.	1.
EPIDIDYMIDES	'	'	(+G	'	'					
- Infiltrate inflamm.			(2.							
- Sperm granuloma			(3.							

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :

	16 MK0	17 MK0	18 MK0	19 MK0	20 MK0	36 FK0	37 FK0	38 FK0	39 FK0	40 FK0
BRAIN	-	-	-	-	-	-	-	-	-	-
SPINAL CORD, CERVIC.	-	-	-	-	-	-	-	-	-	-
SPINAL CORD, THORAC.	-	-	-	-	-	-	-	-	-	-
SPINAL CORD, LUMBAR	-	-	-	-	-	-	-	-	-	-
SCIATIC NERVE, LEFT	-	-	-	-	-	-	-	-	-	-
EYES	-	-	-	-	-	-	-	-	-	-
THYMUS	-	-	-	+	-	-	-	-	-	-
- Lymphocytolysis	.	.	.	1.
MANDIB.LYMPH NODES	-	-	-	-	-	-	-	-	-	-
ADRENAL GLANDS	-	-	-	-	-	-	-	-	-	-
THYROID GLAND	-	-	-	-	-	+	-	-	-	+
- Hypertrophy foll. c.	1.	.	.	.	1.
PARATHYROID GLANDS	-	(-	-	-	-	-	-	-	-
LUNG	-	+	-	+	+	+	-	+	+	+
- Inflamm. peribronch.	.	1.	.	1.	1.	1.	.	1.	1.	2.
- Osseus metaplasia	1.
TRACHEA	-	-	-	-	-	-	-	-	-	-
SKELETAL MUSCLE	-	-	-	-	-	-	-	-	-	-
HEART	-	-	-	-	-	-	-	-	-	-
SPLEEN	-	-	-	-	-	+	+	+	+	-
- Hematopoiesis extra.	1.	.	1.	2.	.
- Pigmentation, hemos.	1.	.	1.	.

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :

	16 MK0	17 MK0	18 MK0	19 MK0	20 MK0	36 FK0	37 FK0	38 FK0	39 FK0	40 FK0
LIVER	-	+	+	-	+	+	+	-G	+	+
- Infiltrate inflamm.	.	1.	1.	.	1.	1.	.	.	1.	1.
- Hypertrophy hepatoc.	1.	1.	.	1.	1.
URINARY BLADDER	-	-	-	-	-	-	-	-	-	-
KIDNEYS	+	-	+	-	-	-	-	-	-	-
- Infiltrate inflamm.	(1.	.	1.
- Hyaline droplet acc.	1.	.	1.
- Basophilia, tubule	(1.
STOMACH	-	-	-	-	-	-	-	-	-	-
DUODENUM	-	-	-	-	-	-	-	-	-	-
JEJUNUM	-	-	-	-	-	-	-	-	-	-
ILEUM	-	-	-	-	-	-	-	-	-	-
PEYER'S PATCHES	-	-	-	-	-	-	-	-	-	-
CECUM	-	-	-	-	-	-	-	-	-	-
COLON	-	-	-	-	-	-	-	-	-	-
RECTUM	-	-	-	-	-	-	-	-	-	-
MESENT. LYMPH NODE	-	-	-	-	-	-	-	-	-	-
SEMINAL VESICLES	-	-	-	-	-	-	-	-	-	-
COAGULATING GLANDS	-	-	-	-	-	-	-	-	-	-
PROSTATE GLAND	-	-	-	-	-	-	-	-	-	-
TESTES	-	+	-	+G	-					
- Atrophy, tubular	.	.	.	5.	.					
- Vacuolation, tubular	.	(1.	.	.	.					

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER :

	16 MK0	17 MK0	18 MK0	19 MK0	20 MK0	36 FK0	37 FK0	38 FK0	39 FK0	40 FK0
EPIDIDYMIDES	-	-	-	+G	-					
- Cell debris, luminal	.	.	.	2.	.					
- Reduced sperm, lum.	.	.	.	5.	.					
.....
OVARIES						-	-	-	-	-
.....
UTERUS						-	-	+G	-	-
- Cyclic dilation						.	.	P.	.	.
.....
CERVIX						-	-	-	-	-
.....
VAGINA						+	+	+	+	+
- Cycle: Proestrus						.	.	P.	.	.
- Cycle: Estrus						.	P.	.	.	P.
- Cycle: Metestrus						P.	.	.	P.	.
.....
BONE, STERNUM	-	-	-	-	-	-	-	-	-	-
.....
BONE MARROW, STERNUM	-	-	+	-	-	-	-	-	-	-
- Increased adipocytes	.	.	1.
.....
BONE, FEMUR	-	-	-	-	-	-	-	-	-	-
.....
JOINT, KNEE, LEFT	-	-	-	-	-	-	-	-	-	-
.....

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 21/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

ANIMAL HEADING DATA
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY
1	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
2	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
3	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
4	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
5	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
.....
21	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
22	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
23	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
24	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
25	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
.....

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 1
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

RECTUM:

Tissue not present for histologic examination

MESENTERIC LYMPH NODE:

-Increased macrophage foci, grade 1

PROSTATE GLAND:

-Infiltrate inflammatory cell, lymphocytic, grade 1

EPIDIDYMIDES:

-Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), TESTES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT).

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 2

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-Inflammation peribronchial/perivasculat, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

KIDNEYS:

-Basophilia, tubule, unilateral, grade 1

PROSTATE GLAND:

-Infiltrate inflammatory cell, lymphocytic, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 3
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

HEART:

-Infiltrate inflammatory cell, lymphocytic, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

KIDNEYS:

-Hyaline droplet accumulation, bilateral, grade 2

EPIDIDYMIDES:

-Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, BONE (STERNUM) , BONE MARROW (STERNUM) , BONE (FEMUR) , JOINT (KNEE, LEFT) .

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 4
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-Inflammation peribronchial/perivascular, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PROSTATE GLAND:

-Infiltrate inflammatory cell, lymphocytic, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), TESTES, EPIDIDYMIDES, BONE (STERNUM) , BONE MARROW (STERNUM) , BONE (FEMUR) , JOINT (KNEE, LEFT) .

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 5

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYMUS:

-Lymphocytolysis, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

KIDNEYS:

-Basophilia, tubule, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 21
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-Inflammation peribronchial/perivasculat, grade 1

TRACHEA:

-Infiltrate inflammatory cell, lymphocytic, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

VAGINA:

-Cycle: diestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM) , BONE MARROW (STERNUM), BONE (FEMUR) , JOINT (KNEE, LEFT) .

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 22
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYMUS:

-Lymphocytolysis, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

LUNG:

-Inflammation peribronchial/perivascular, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

VAGINA:

-Cycle: diestrus

BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, SPLEEN, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 29/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 23
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

- Alveolar macrophage aggregation, grade 1
- Inflammation peribronchial/perivasculat, grade 1

SPLEEN:

- Hematopoiesis, extramedullary, grade 1
- Pigmentation, hemosiderin, grade 1

LIVER:

- Infiltrate inflammatory cell, lymphocytic, grade 1

VAGINA:

- Cycle: metestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 24
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
LIVER:
-Infiltrate inflammatory cell, lymphocytic, grade 1
VAGINA:
-Cycle: metestrus
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, PARATHYROID GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 31/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 25
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPINAL CORD (LUMBAR SEGMENT) :

Tissue not present for histologic examination

THYROID GLAND (BOTH LOBES) :

-Hypertrophy follicular cell, bilateral, grade 1

PARATHYROID GLANDS:

Only one of paired organs examined/present

LUNG:

-Inflammation peribronchial/perivascular, grade 1

TRACHEA:

-Ectasia submucosal glands, grade 1

SPLEEN:

-Pigmentation, hemosiderin, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

KIDNEYS:

-Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1

STOMACH:

-Cyst(s), glandular, grade 1

VAGINA:

-Cycle: metestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 32/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

FEMALE

CONT./FF. ANIMAL NO. : 25

.....

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, PARATHYROID GLANDS, SKELETAL MUSCLE, HEART, URINARY BLADDER, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .
-

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 33/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

ANIMAL HEADING DATA

DOSE GROUP : 02, 100 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY
6	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
7	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
8	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
9	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
10	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
.....
26	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
27	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
28	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
29	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
30	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
.....

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 34/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 6
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-Hematopoiesis, extramedullary, grade 1

* STATE AT NECROPSY: K0 * ANIMAL NO. : 7
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-Hematopoiesis, extramedullary, grade 2

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 35/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG

MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 8

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-Hematopoiesis, extramedullary, grade 1

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 9

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-Hematopoiesis, extramedullary, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 36/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG

MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 10

* NECROPSY FINDINGS

EPIDIDYMIIDES:

01: TAIL, RIGHT SIDE: NODULE(S), D=8X4 MM, YELLOWISH, HARD.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

EPIDIDYMIIDES:

Only one of paired organs examined/present

-Sperm granuloma, unilateral, grade 4

This finding corresponds to necropsy observation no: 01.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 37/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG

FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 26

* NECROPSY FINDINGS

UTERUS:
01: CONTAINS FLUID.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

LIVER:
-Infiltrate inflammatory cell, lymphocytic, grade 1
UTERUS:
-Cyclic dilation
This finding corresponds to necropsy observation no: 01.
CERVIX:
Organ examined, no pathologic findings noted
VAGINA:
-Cycle: estrus

* ORGANS WITHOUT ABNORMALITIES

- CERVIX.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 38/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG

FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 27

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 28

* NECROPSY FINDINGS

ADRENAL GLANDS:

01: BOTH SIDES: ENLARGED.

NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:

No microscopic finding corresponding to necropsy observation no. 01.
-Vacuolation zona fasciculata, bilateral, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 39/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 29
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-Infiltrate inflammatory cell, lymphocytic, grade 1

* STATE AT NECROPSY: K0 * ANIMAL NO. : 30
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

ADRENAL GLANDS:
01: BOTH SIDES: ENLARGED.
UTERUS:
01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

ADRENAL GLANDS:
No microscopic finding corresponding to necropsy observation no. 01.
LIVER:
-Infiltrate inflammatory cell, lymphocytic, grade 1
UTERUS:
-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 40/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 30

.....

VAGINA:

-Cycle: proestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- ADRENAL GLANDS, CERVIX.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 41/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

ANIMAL HEADING DATA
DOSE GROUP : 03, 300 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY
11	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
12	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
13	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
14	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
15	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
31	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
32	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
33	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
34	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
35	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 42/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 11
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
Organ examined, no pathologic findings noted

* ORGANS WITHOUT ABNORMALITIES

- SPLEEN.

* STATE AT NECROPSY: K0 * ANIMAL NO. : 12
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:
-Hematopoiesis, extramedullary, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 43/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG

MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28 * ANIMAL NO. : 13
.....

* NECROPSY FINDINGS

EPIDIDYMIIDES:

01: TAIL, LEFT SIDE: NODULE(S), D=7X8 MM, YELLOWISH, SOFT.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

SPLEEN:

-Hematopoiesis, extramedullary, grade 1
-Pigmentation, hemosiderin, grade 1

EPIDIDYMIIDES:

Only one of paired organs examined/present
-Infiltrate inflammatory cell, lymphocytic, unilateral, grade 2
-Sperm granuloma, unilateral, grade 3
This finding corresponds to necropsy observation no: 01.

* STATE AT NECROPSY: K0
DAYS ON TEST : 28 * ANIMAL NO. : 14
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 44/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG

MALE

CONT./FF. ANIMAL NO. : 14

.....

* MICROSCOPIC FINDINGS

SPLEEN:

Organ examined, no pathologic findings noted

* ORGANS WITHOUT ABNORMALITIES

- SPLEEN.

* STATE AT NECROPSY: K0 * ANIMAL NO. : 15
DAYS ON TEST : 28

.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 45/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG

FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 31

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 32

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 46/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG

FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 33

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 34

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 47/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 MG/KG

FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 35

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 48/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

ANIMAL HEADING DATA

DOSE GROUP : 04, 1000 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY
16	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
17	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
18	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
19	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
20	M	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
36	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
37	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
38	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
39	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16
40	F	K0	28	14-OCT-16	10-NOV-16	11-NOV-16

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 16
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

- Infiltrate inflammatory cell, lymphocytic, unilateral, grade 1
- Hyaline droplet accumulation, bilateral, grade 1
- Basophilia, tubule, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, SPLEEN, LIVER, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM) , BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .
-

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 17
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

PARATHYROID GLANDS:

Only one of paired organs examined/present

LUNG:

-Inflammation peribronchial/perivasculat, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

TESTES:

-Vacuolation, tubular, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, SPLEEN, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, EPIDIDYMIDES, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .
-

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 18
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

KIDNEYS:

-Infiltrate inflammatory cell, lymphocytic, bilateral, grade 1

-Hyaline droplet accumulation, bilateral, grade 1

BONE MARROW (STERNUM):

-Increased adipocytes, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, SPLEEN, URINARY BLADDER, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM) , BONE (FEMUR) , JOINT (KNEE, LEFT) .
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PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 52/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

MALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 19
DAYS ON TEST : 28
.....

* NECROPSY FINDINGS

TESTES:
01: BOTH SIDES: REDUCED IN SIZE.
EPIDIDYMIDES:
01: BOTH SIDES: REDUCED IN SIZE.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

THYMUS:
-Lymphocytolysis, grade 1
LUNG:
-Inflammation peribronchial/perivasculat, grade 1
TESTES:
-Atrophy, tubular, bilateral, grade 5
This finding corresponds to necropsy observation no: 01.
EPIDIDYMIDES:
-Cell debris, luminal, bilateral, grade 2
-Reduced sperm, luminal, bilateral, grade 5
This finding corresponds to necropsy observation no: 01.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

MALE

CONT./FF. ANIMAL NO. : 19

.....

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, SPLEEN, LIVER, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

* STATE AT NECROPSY: K0 * ANIMAL NO. : 20
DAYS ON TEST : 28

.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-Inflammation peribronchial/perivascular, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

MALE

CONT./FF. ANIMAL NO. : 20

.....

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, SPLEEN, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, SEMINAL VESICLES, COAGULATING GLANDS (ANTERIOR PROSTATE), PROSTATE GLAND, TESTES, EPIDIDYMIDES, BONE (STERNUM) , BONE MARROW (STERNUM) , BONE (FEMUR) , JOINT (KNEE, LEFT).
-

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 36
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 1
LUNG:
-Inflammation peribronchial/perivasculat, grade 1
-Osseus metaplasia, grade 1
SPLEEN:
-Hematopoiesis, extramedullary, grade 1
LIVER:
-Infiltrate inflammatory cell, lymphocytic, grade 1
-Hypertrophy, hepatocellular, grade 1
VAGINA:
-Cycle: metestrus
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 56/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

FEMALE

* STATE AT NECROPSY: K0 * ANIMAL NO. : 37
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

SPLEEN:

-Pigmentation, hemosiderin, grade 1

LIVER:

-Hypertrophy, hepatocellular, grade 1

VAGINA:

-Cycle: estrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, LUNG, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 57/ 60
TOX : 514867

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 28

* ANIMAL NO. : 38

* NECROPSY FINDINGS

LIVER:

01: PAPILLARY PROCESS, LEFT SIDE: REDUCED IN SIZE.

UTERUS:

01: CONTAINS FLUID.

NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

LUNG:

-Inflammation peribronchial/perivascular, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, grade 1

LIVER:

No microscopic finding corresponding to necropsy observation no. 01.

UTERUS:

-Cyclic dilation

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Cycle: proestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 38

.....

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, LIVER, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

* STATE AT NECROPSY: K0
DAYS ON TEST : 28 * ANIMAL NO. : 39

.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LUNG:

-Inflammation peribronchial/perivascular, grade 1

SPLEEN:

-Hematopoiesis, extramedullary, grade 2

-Pigmentation, hemosiderin, grade 1

LIVER:

-Infiltrate inflammatory cell, lymphocytic, grade 1

-Hypertrophy, hepatocellular, grade 1

VAGINA:

-Cycle: metestrus

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

TEST ITEM : MLA-3202
TEST SYSTEM : RAT, 28-d, Oral gavage
SPONSOR : Chemtura Corporation

PATHOL. NO.: 41639 JOL
FINALIZED : 27-FEB-17
PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 39

.....

* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, THYROID GLAND (BOTH LOBES), PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .

* STATE AT NECROPSY: K0
DAYS ON TEST : 28 * ANIMAL NO. : 40

.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

THYROID GLAND (BOTH LOBES):
-Hypertrophy follicular cell, bilateral, grade 1
LUNG:
-Inflammation peribronchial/perivascular, grade 2
LIVER:
-Infiltrate inflammatory cell, lymphocytic, grade 1
-Hypertrophy, hepatocellular, grade 1
VAGINA:
-Cycle: estrus
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT (FINAL)
INDIVIDUAL ANIMAL DATA

PAGE : 60/ 60
TOX : 514867

TEST ITEM : MLA-3202 PATHOL. NO.: 41639 JOL
TEST SYSTEM : RAT, 28-d, Oral gavage FINALIZED : 27-FEB-17
SPONSOR : Chemtura Corporation PathData®System V6.2e2

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 40

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* ORGANS WITHOUT ABNORMALITIES

- BRAIN, SPINAL CORD (CERVICAL SEGMENT), SPINAL CORD (THORACIC SEGMENT), SPINAL CORD (LUMBAR SEGMENT), SCIATIC NERVE (LEFT) , EYES, THYMUS, MANDIBULAR LYMPH NODES, ADRENAL GLANDS, PARATHYROID GLANDS, TRACHEA, SKELETAL MUSCLE, HEART, SPLEEN, URINARY BLADDER, KIDNEYS, STOMACH, DUODENUM, JEJUNUM, ILEUM, PEYER'S PATCHES, CECUM, COLON, RECTUM, MESENTERIC LYMPH NODE, OVARIES, UTERUS, CERVIX, BONE (STERNUM), BONE MARROW (STERNUM), BONE (FEMUR), JOINT (KNEE, LEFT) .
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APPENDIX 5
SUMMARY OF DOSE RANGE FINDING STUDY

Summary of Dose Range Finding Study

If not mentioned otherwise, test system, procedures and techniques were identical to those used during the main study.

All activities of the dose range finder were performed at the 's-Hertogenbosch location.

Time schedule and responsible personnel

Treatment	19 September 2016 to 23 September 2016
Necropsy	M. Schelling (Charles River Den Bosch)
Coordination Biotechnician	W. Uijtdewilligen (Charles River Den Bosch)

Purpose

A Dose Range Finding Study was performed to select dose levels for the main study (Test Facility Study No. 514867) and to determine the peak effect of occurrence of clinical signs after dosing.

Guidelines

No guidelines were applicable as this study was intended for dose level selection purposes only.

Test System/Animal husbandry

Number of rats	6 females.
Age at start of treatment	Approximately 6 weeks.
Identification	Earmark and tailmark.
Randomisation	Animals were allocated at random at the discretion of the biotechnician. Body weight variation did not exceed \pm 20% of the main.
Room number	A0.61b.
Housing	3 animals/cage.

Treatment

Method	The dose control system (DCS) was used to verify the dosing procedure.
Duration of treatment	5 days
Dose levels	500 and 1000 mg/kg body weight
	Dose levels were based on the results of the acute oral toxicity study (Test Facility Study No. 511876).
	No chemical analyses of dose preparations were conducted. Homogeneity and stability of the test item under test conditions was demonstrated in the analytical method development and validation study (Test Facility Study No. 514869).
Dose volume	5 mL/kg body weight.
Vehicle	Water (Elix, Millipore S.A.S., Molsheim, France)

Observations

Mortality	At least twice daily.
Clinical signs	Daily, at least at 0-15 minutes, 1 hour (\pm 15 minutes) and 3 hours (\pm 30 minutes) after dosing.
Body weights	On Day 1 prior to dosing and on Days 5.
Food consumption	Over Days 1-5.

Pathology

Necropsy	All animals were subjected to an external, thoracic and abdominal examination on Day 5 after the last observation of clinical signs (scheduled necropsy). No organs were fixed. Animals were not deprived of food prior to necropsy.
Organ weights	Terminal body weight, kidney, and liver weight (at scheduled sacrifice).

Results

Parameter	500 mg/kg	1000 mg/kg
Mortality	No mortality.	No mortality.
Clinical appearance	Salivation: one animal on Day 5 only.	Salivation: All animals on Days 4 and/or 5.
Body weight	Normal.	Normal.
Food consumption	Normal.	Normal.
Macroscopic examination	No abnormalities noted.	No abnormalities noted.

Conclusion

Based on the results of the range finding study, the suggested dose levels for the main study are 100, 300 and 1000 mg/kg.

No clear peak effect of occurrence of clinical signs was observed in the range finding study. As a result, clinical observations in the main study will be conducted immediately after dosing, and functional observation tests will be conducted after dosing at no specific time point but within a similar time period after dosing for the respective animals.

APPENDIX 6
CERTIFICATE OF PURITY



Chemtura Corporation
12 Spencer St.
Naugatuck, CT 06770

Analytical Services
www.chemtura.com

Certificate of Purity

Customer: Support for Toxicology Studies

Test Substance Name: MLA3202; Amides, tallow, N,N-bis(2-hydroxypropyl)

Physical Appearance: Liquid

CAS No.: 1454803-04-3

Ref. or Lot Number: RC-1045

Date of Analysis: revised March 18, 2016 (original issue March 7, 2016)

Percent Composition	Monoisotopic Mass (daltons)	Formula	Structure/ Identity
33.1	397.4	C ₂₄ H ₄₇ NO ₃	C18:1 (oleic) tallow amides, N,N-bis(2-hydroxypropyl)
22.9	371.3	C ₂₂ H ₄₅ NO ₃	C16:0 (palmitic) tallow amides, N,N-bis(2-hydroxypropyl)
13.6	395.4	C ₂₄ H ₄₅ NO ₃	C18:2 (linoleic) tallow amides, N,N-bis(2-hydroxypropyl)
11.0	399.4	C ₂₄ H ₄₉ NO ₃	C18:0 (stearic) tallow amides, N,N-bis(2-hydroxypropyl)
6.0	369.3	C ₂₂ H ₄₃ NO ₃	C16:1 (palmitoleic) tallow amides, N,N-bis(2-hydroxypropyl)
3.2	419.3	C ₂₆ H ₄₅ NO ₃	C20:4 (eicosatetraenoic) tallow amides, N,N-bis(2-hydroxypropyl)
2.0	393.3	C ₂₄ H ₄₃ NO ₃	C18:3 (linolenic) tallow amides, N,N-bis(2-hydroxypropyl)
1.5	282.3	C ₁₈ H ₃₄ O ₂	C18:1 (oleic) acid
1.1	421.4	C ₂₆ H ₄₇ NO ₃	C20:3 (eicosatrienoic) tallow amides, N,N-bis(2-hydroxypropyl)
5.6			Sum of residual components (< 1% each)
100.0			Total

Blake Lewis 3/7/16
 Blake Lewis
 Analytical REACH Scientist, Analytical Services

Colin Moore 3/7/16
 Colin Moore
 Sr. Technology Manager
 Analytical and Lab Support Services